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(54) **METHOD OF EVALUATING A TREATMENT FOR VASCULAR DISEASE**

(75) Inventor: **John B. Simpson**, Woodside, CA (US)

Correspondence Address:
BANNER & WITCOFF
1001 G STREET N W
SUITE 1100
WASHINGTON, DC 20001 (US)

(73) Assignee: **Fox Hollow Technologies, Inc.**, Redwood City, CA

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Related U.S. Application Data

(63) Continuation-in-part of application No. 11/199,370, filed on Aug. 9, 2005, which is a continuation-in-part of application No. 11/010,833, filed on Dec. 13, 2004, and which is a continuation-in-part of application No. 10/896,741, filed on Jul. 21, 2004, which is a continuation-in-part of application No. 10/288,559, filed on Nov. 4, 2002, which is a continuation-in-part of application No. 10/027,418, filed on Dec. 19, 2001.

(60) Provisional application No. 60/257,704, filed on Dec. 20, 2000. Provisional application No. 60/272,273, filed on Feb. 27, 2001. Provisional application No. 60/381,632, filed on May 17, 2002.

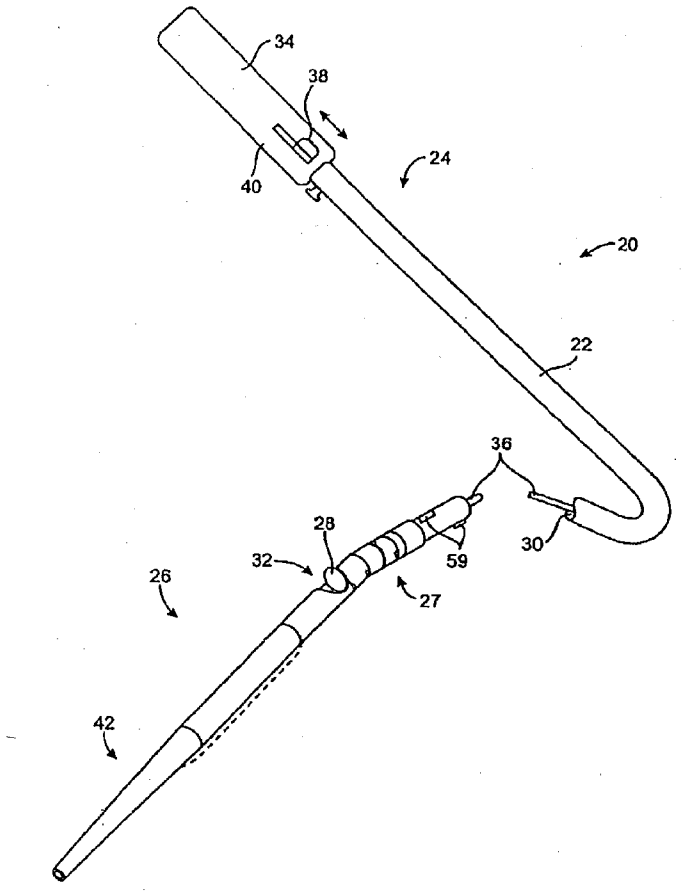
Publication Classification

(51) **Int. Cl.**
A61M 31/00 (2006.01)
A61F 2/06 (2006.01)

(52) **U.S. Cl.** **604/508**; 623/1.11

(57) **ABSTRACT**

Methods of evaluating treatments for vascular disease are described. The treatments can include administration of pharmaceutical, chemical, or biological agents. Vascular tissue is removed from a first site in a vascular lumen and optionally analyzed. A treatment is administered to the patient, followed by removal of a second portion of vascular tissue from a second site. The vascular tissue from both the first and second site are compared to learn the effect of the treatment. Treatments can include placement of prosthetic devices such as stents in the lumen. Whether or not the vascular tissue recurs at a site after removal can be monitored as a measure of the success of a given treatment.



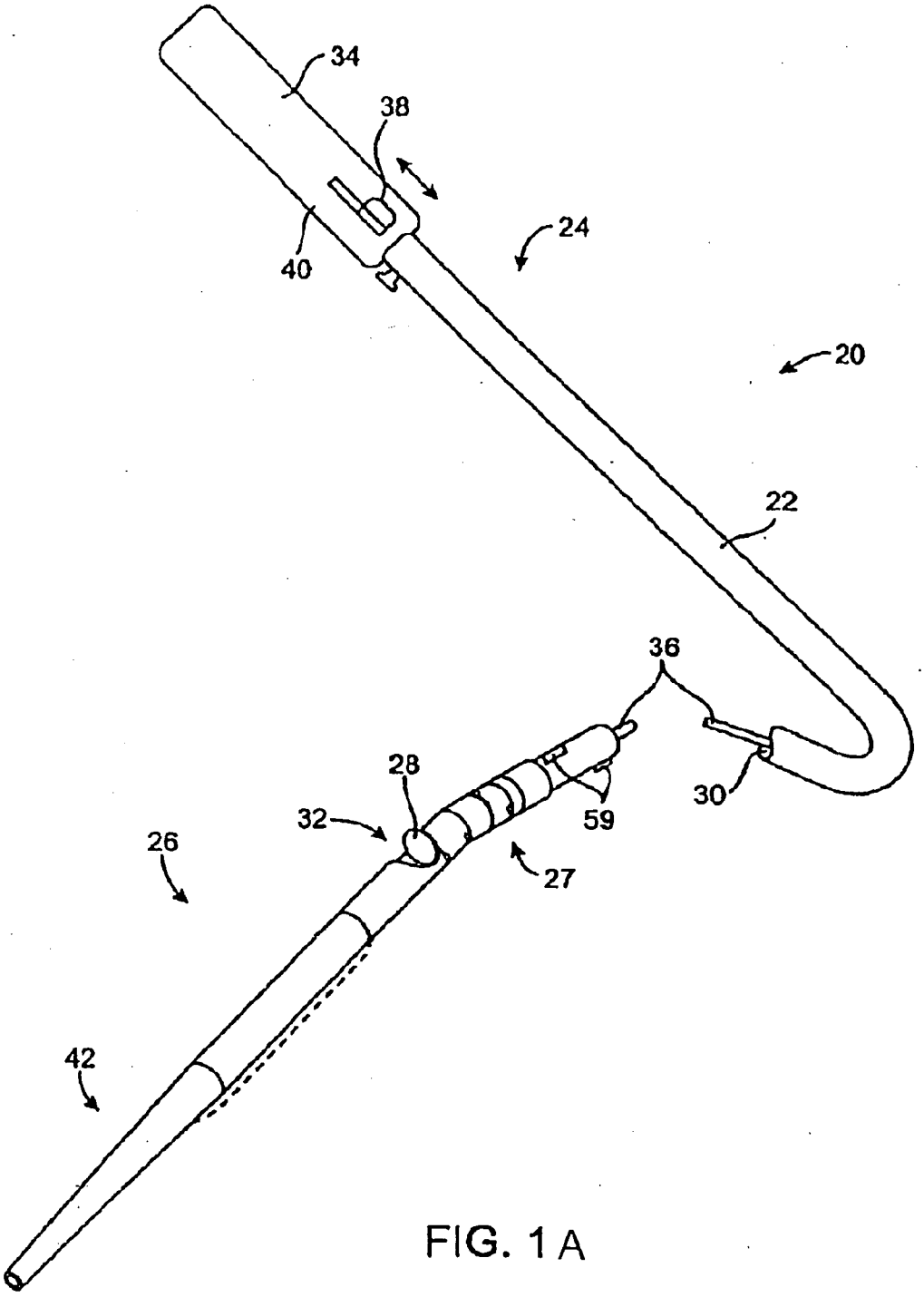


FIG. 1A

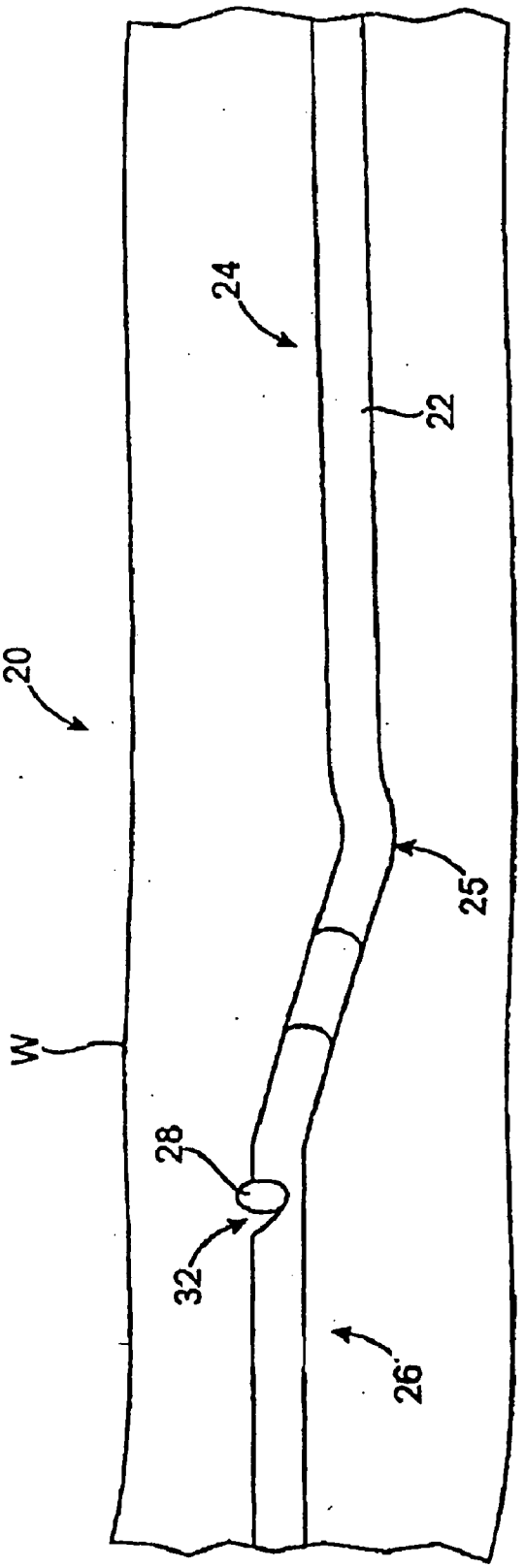


FIG. 1B

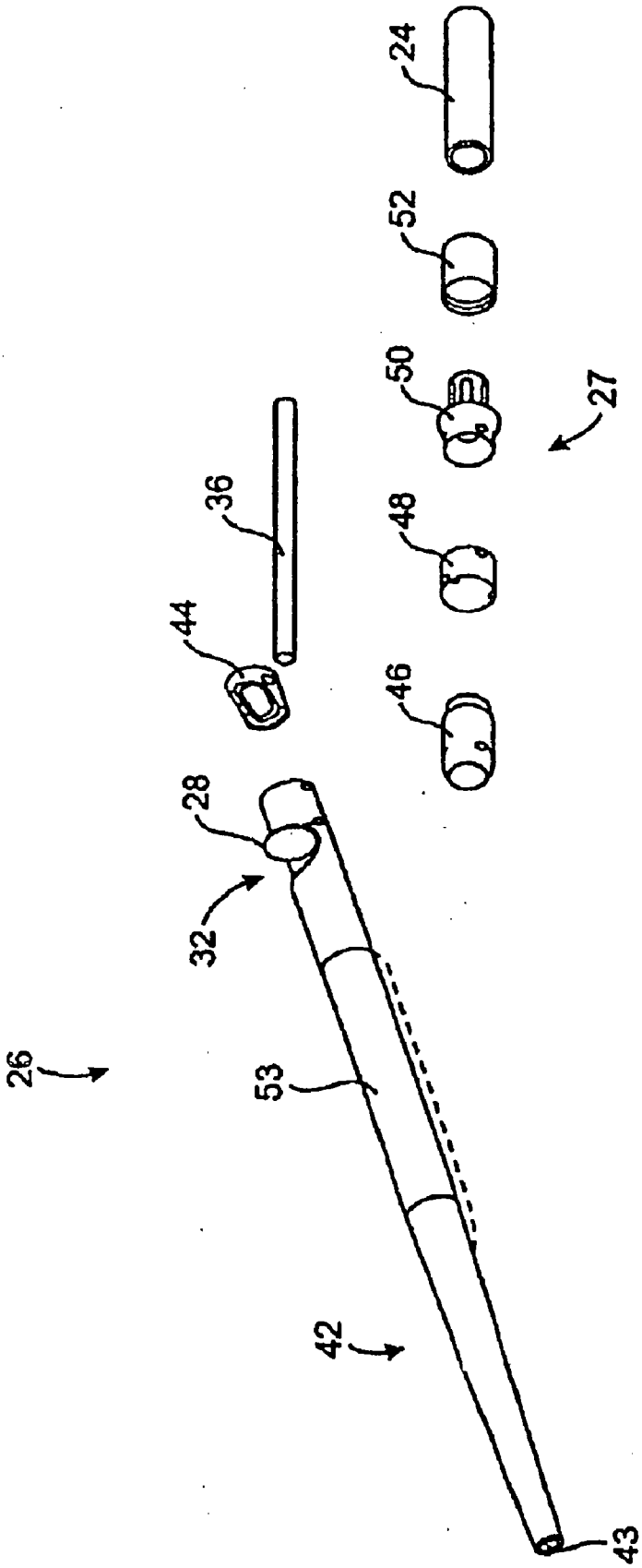


FIG. 2

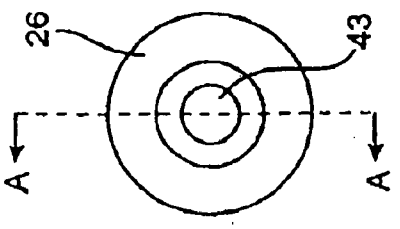


FIG. 3A

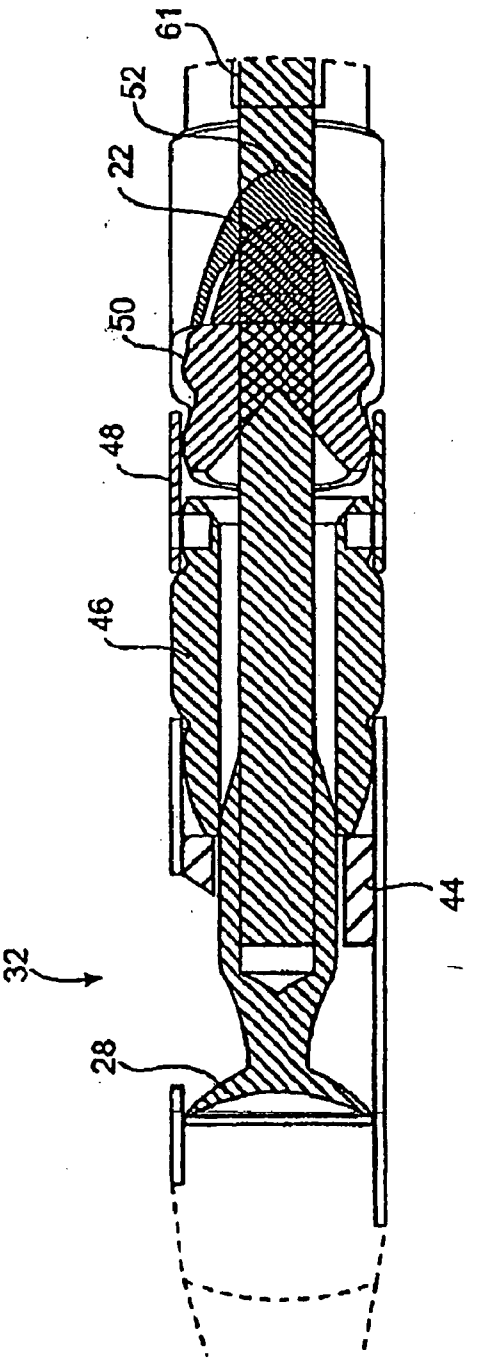


FIG. 3B

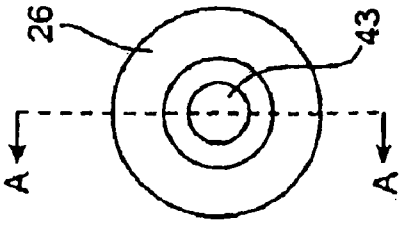


FIG. 3C

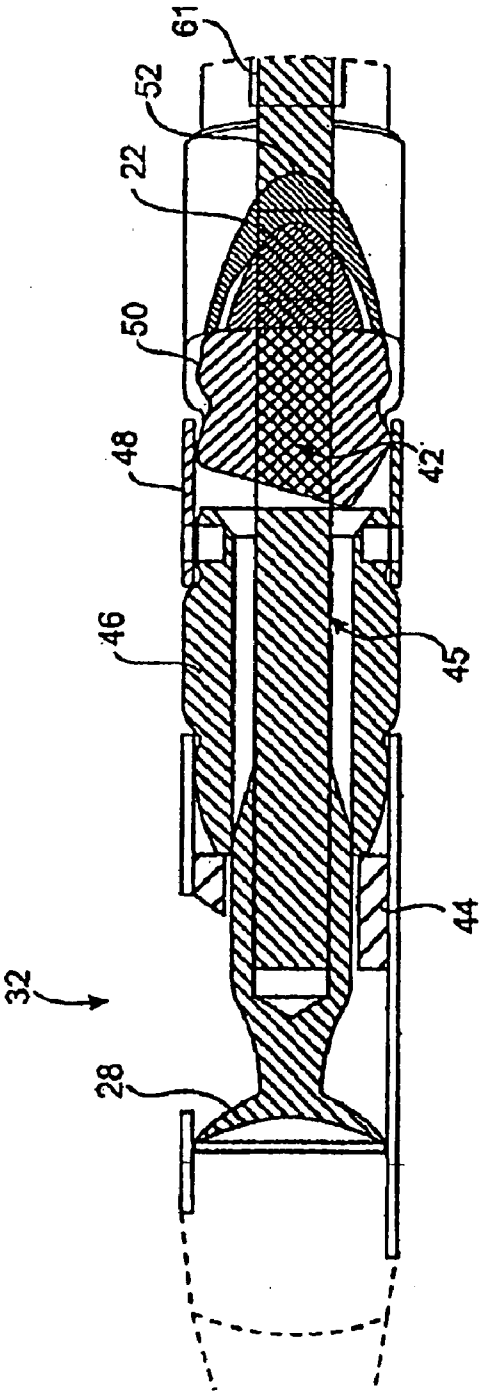


FIG. 3D

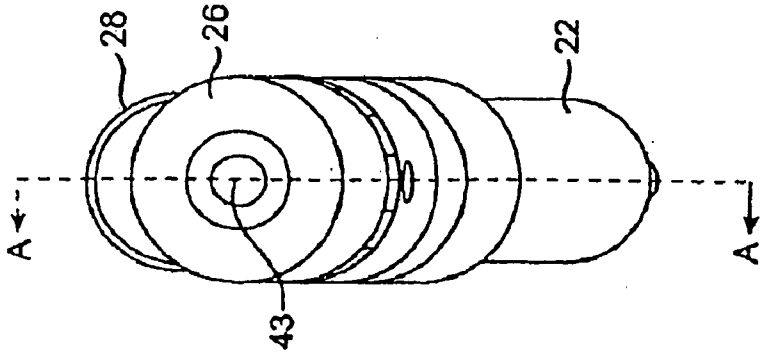


FIG. 4A

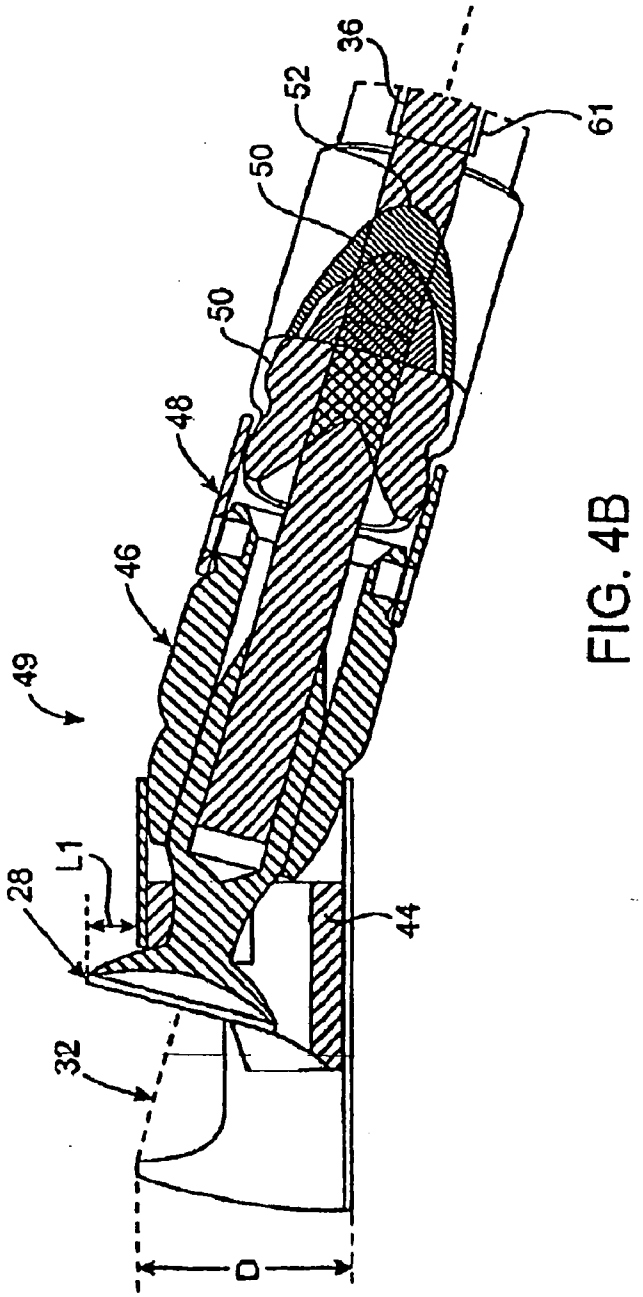


FIG. 4B

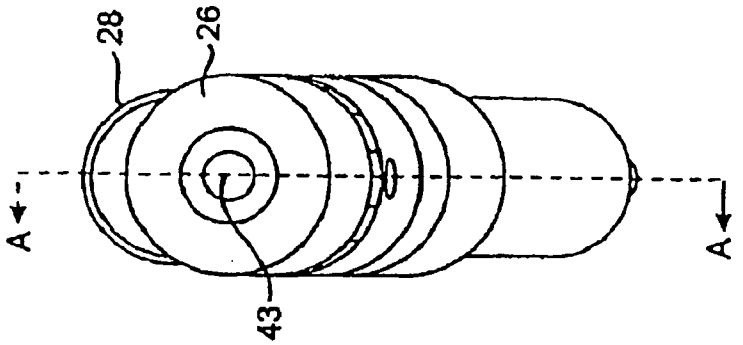


FIG. 4C

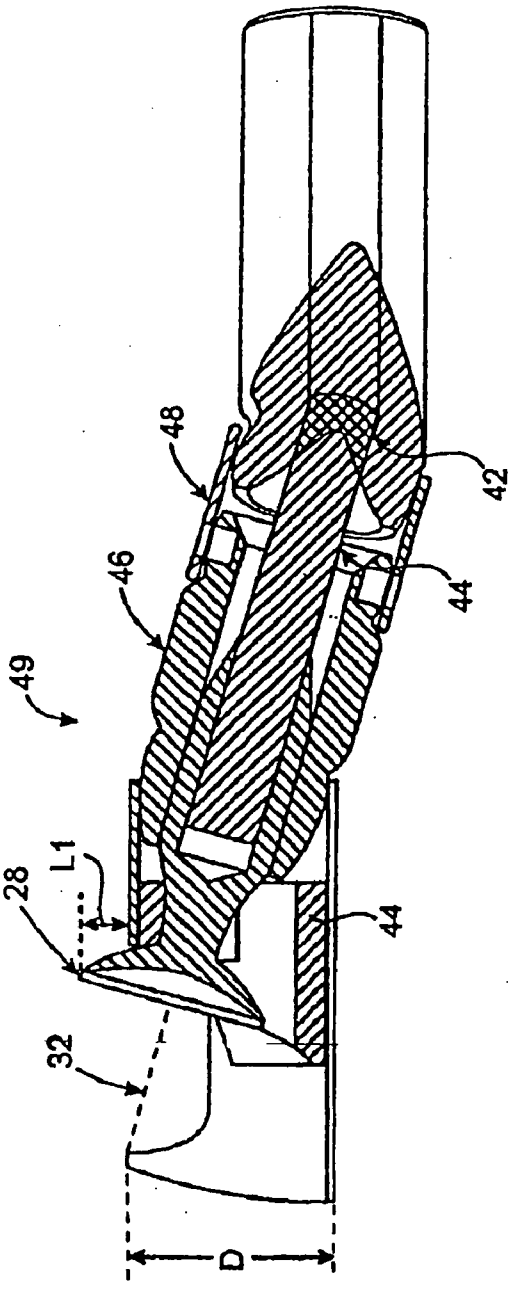


FIG. 4D

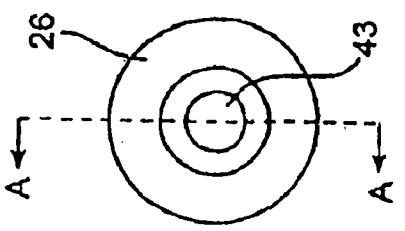


FIG. 5A

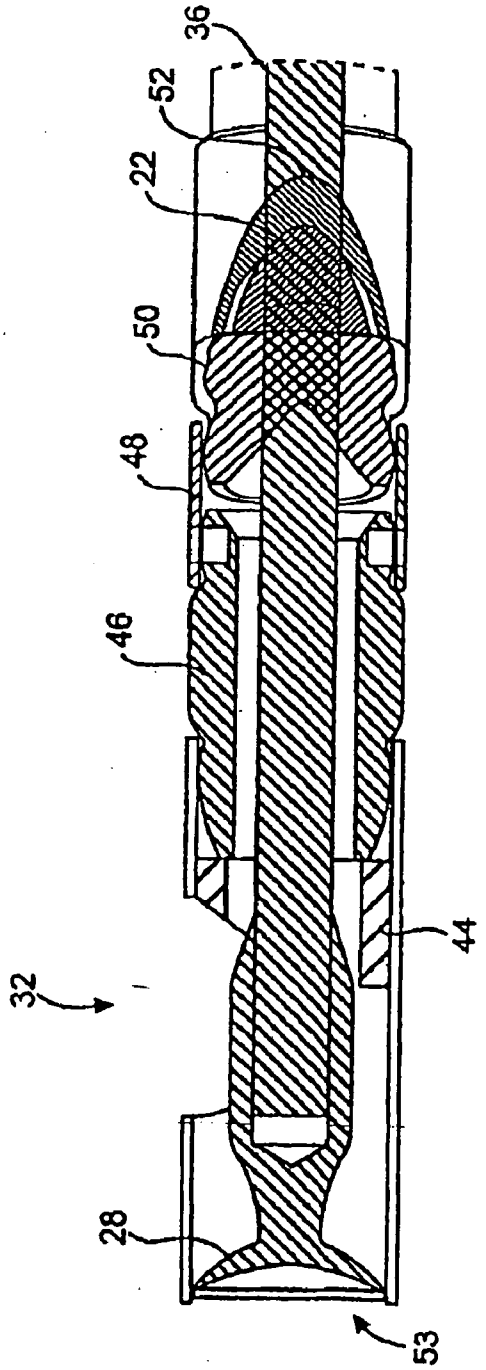


FIG. 5B

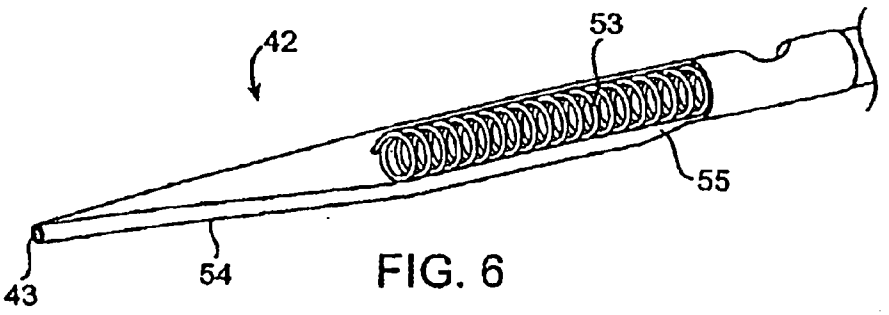


FIG. 6

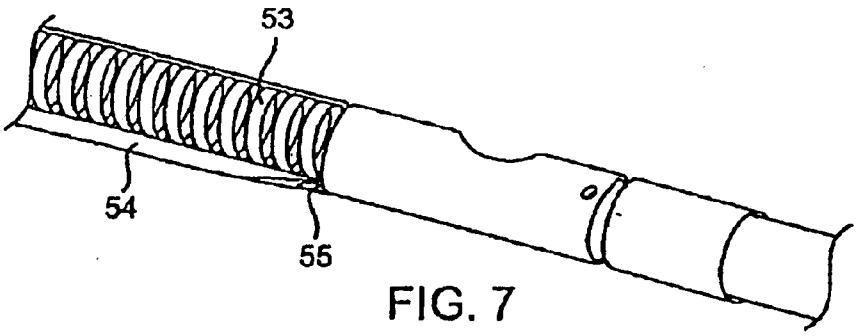


FIG. 7

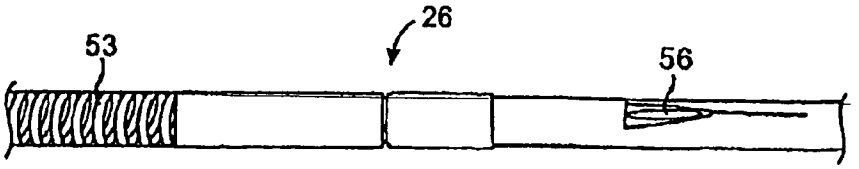


FIG. 8

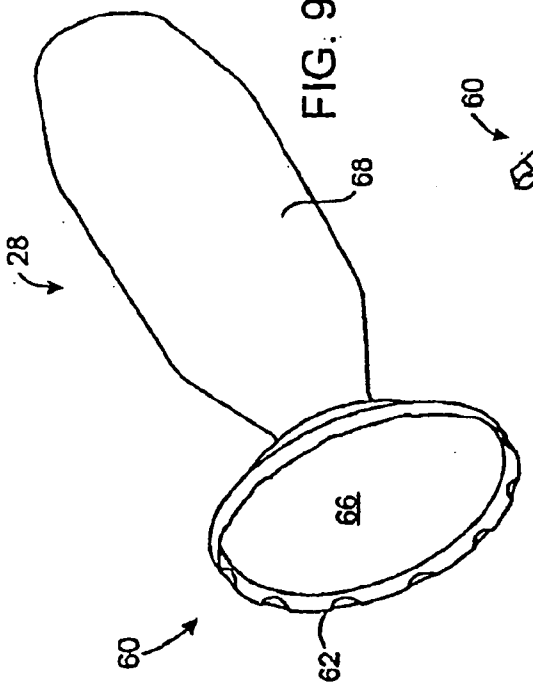


FIG. 9A

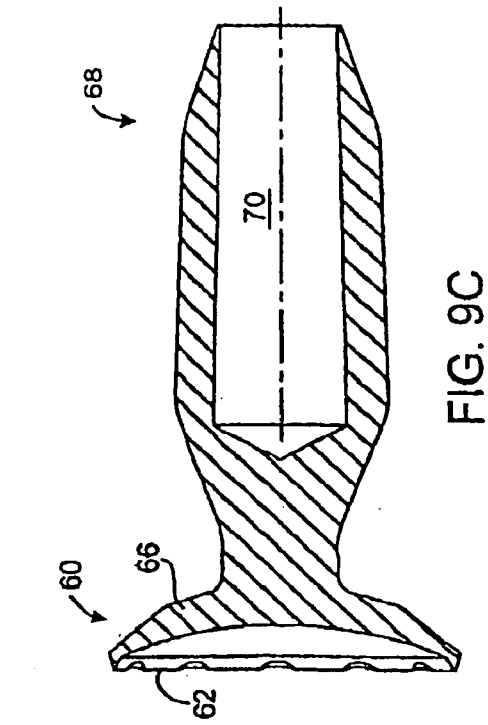


FIG. 9C

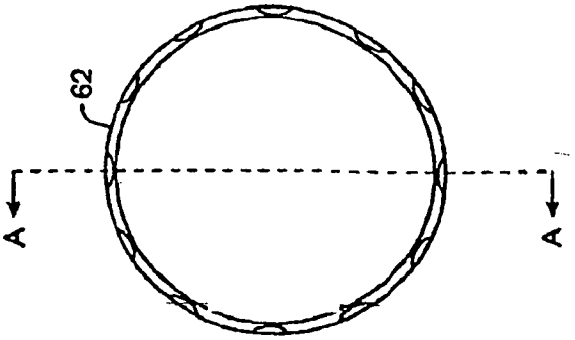


FIG. 9B

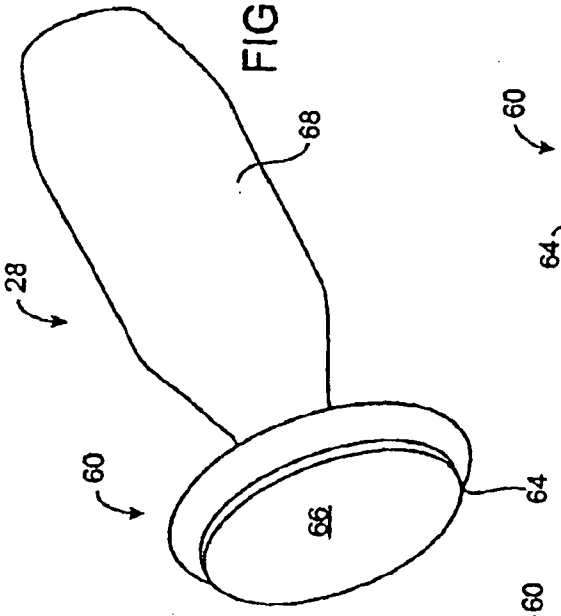


FIG. 10A

FIG. 10B

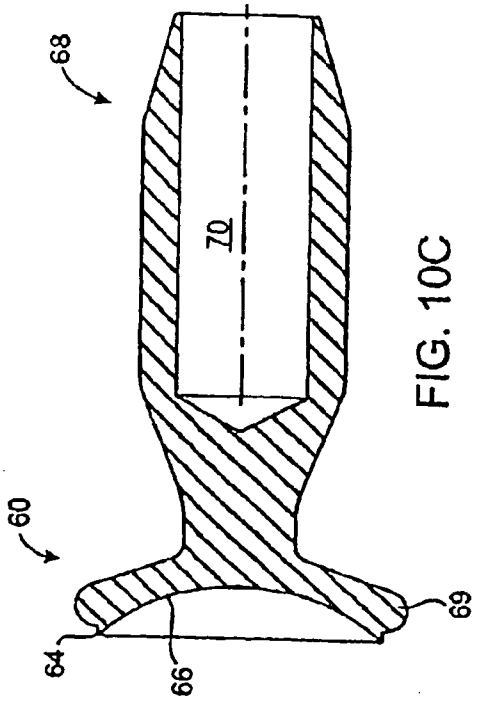


FIG. 10C

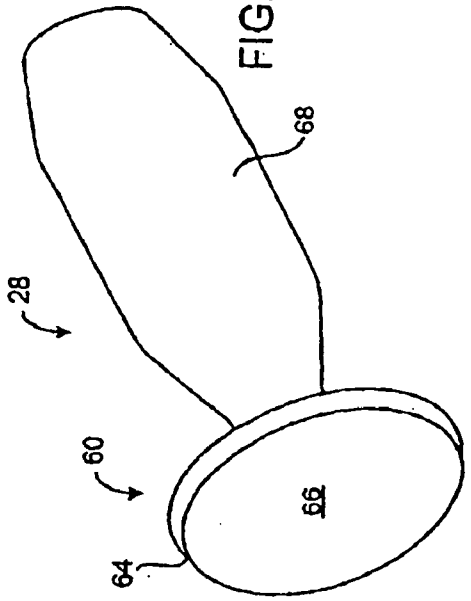


FIG. 11A

FIG. 11B

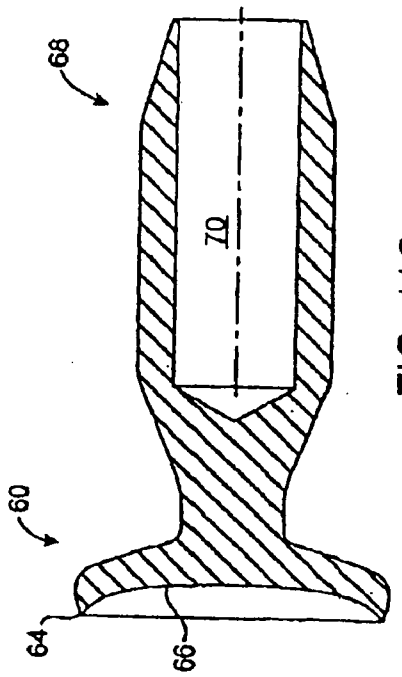


FIG. 11C

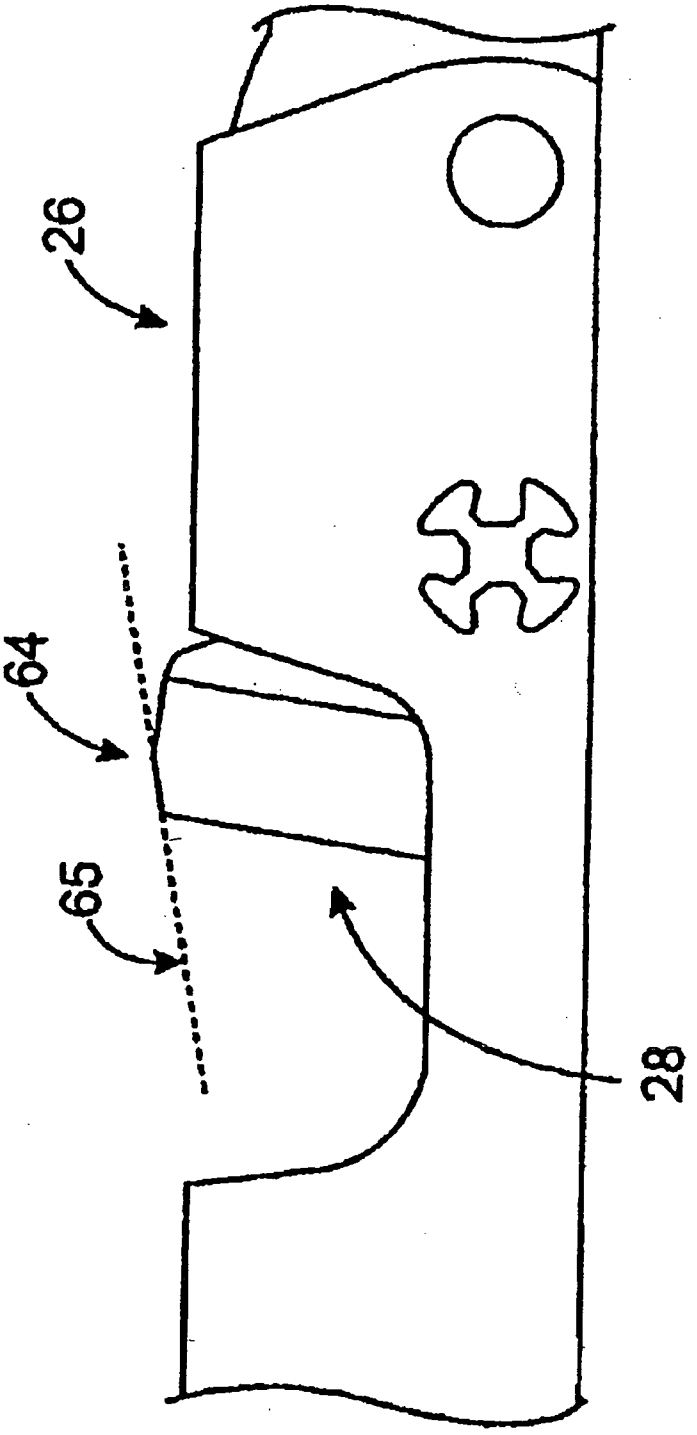


FIG. 11D

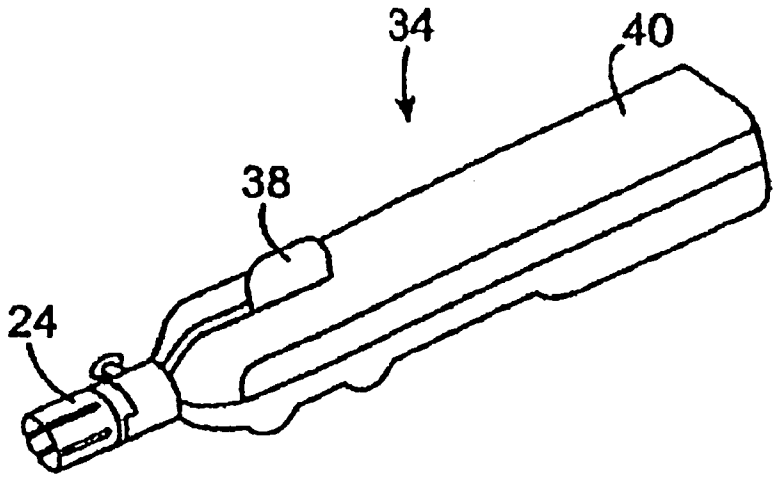


FIG. 12

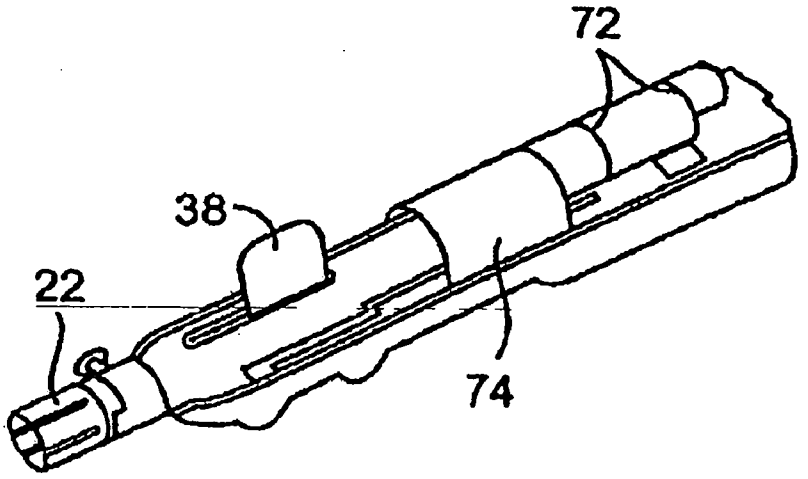


FIG. 13

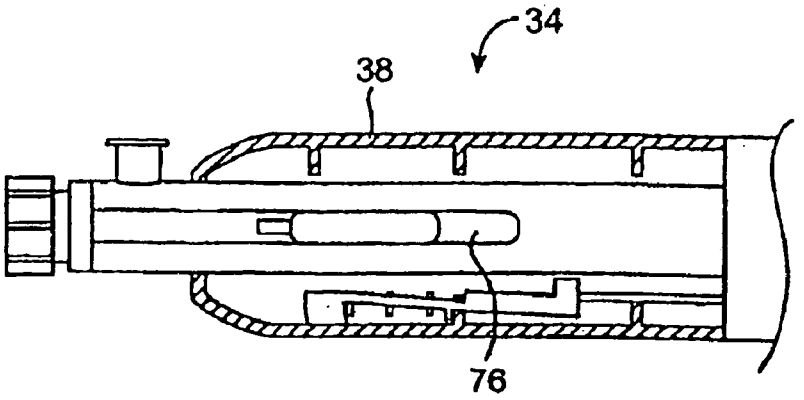


FIG. 14

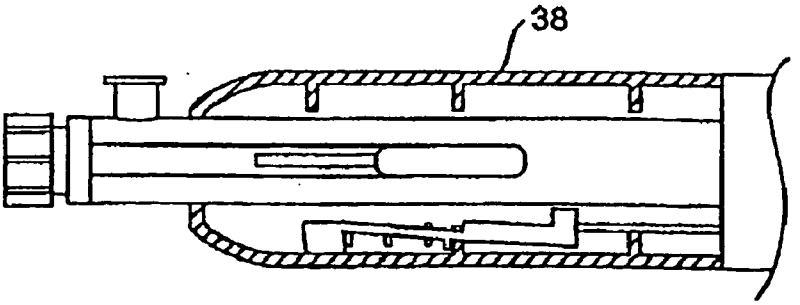


FIG. 15

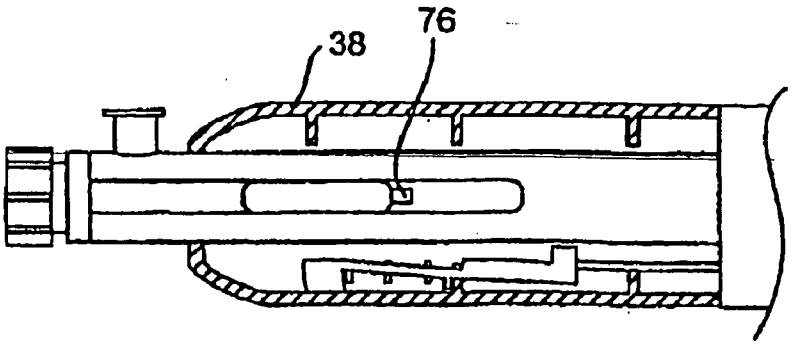


FIG. 16

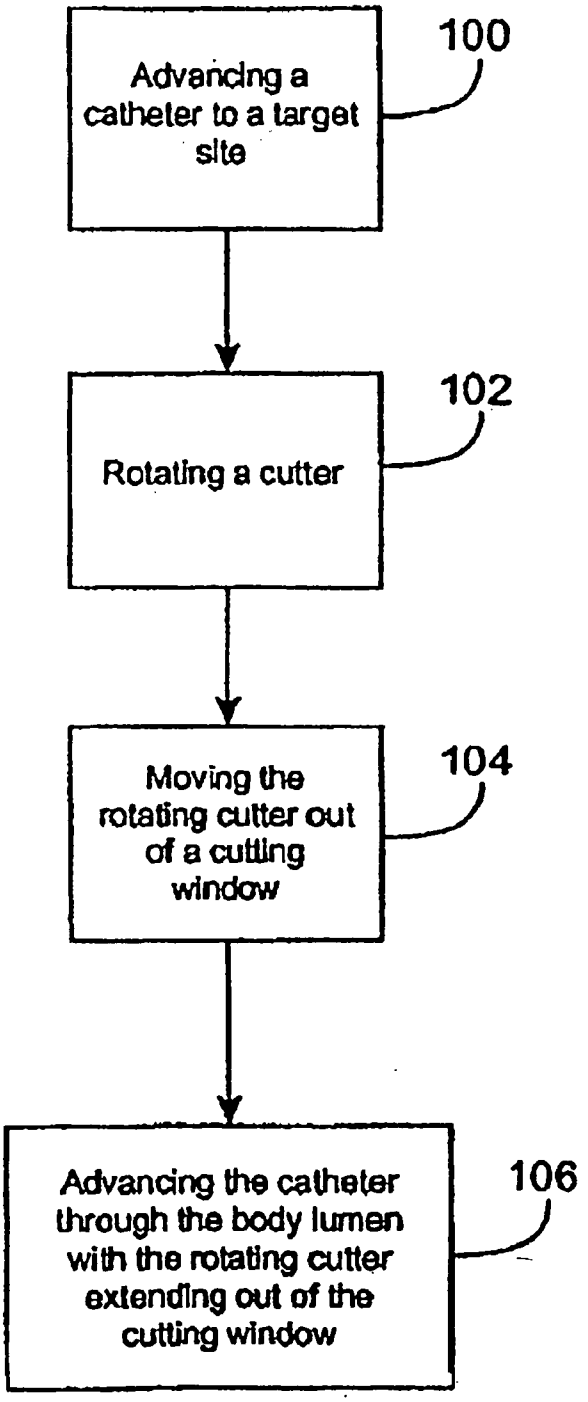

Advancing a catheter to a target site
100
Rotating a cutter
102
Moving the rotating cutter out of a cutting window
104
Advancing the catheter through the body lumen with the rotating cutter extending out of the cutting window
106

FIG. 17

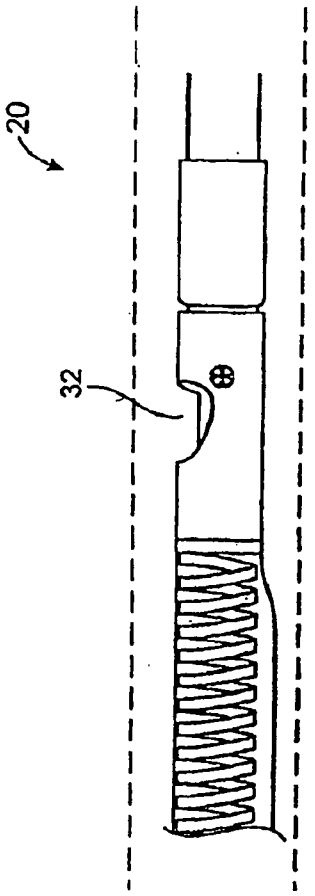


FIG. 18

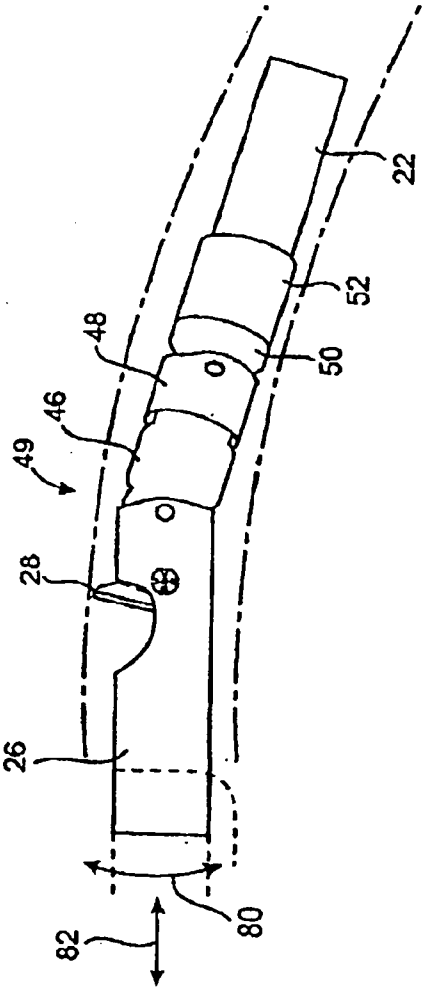


FIG. 19

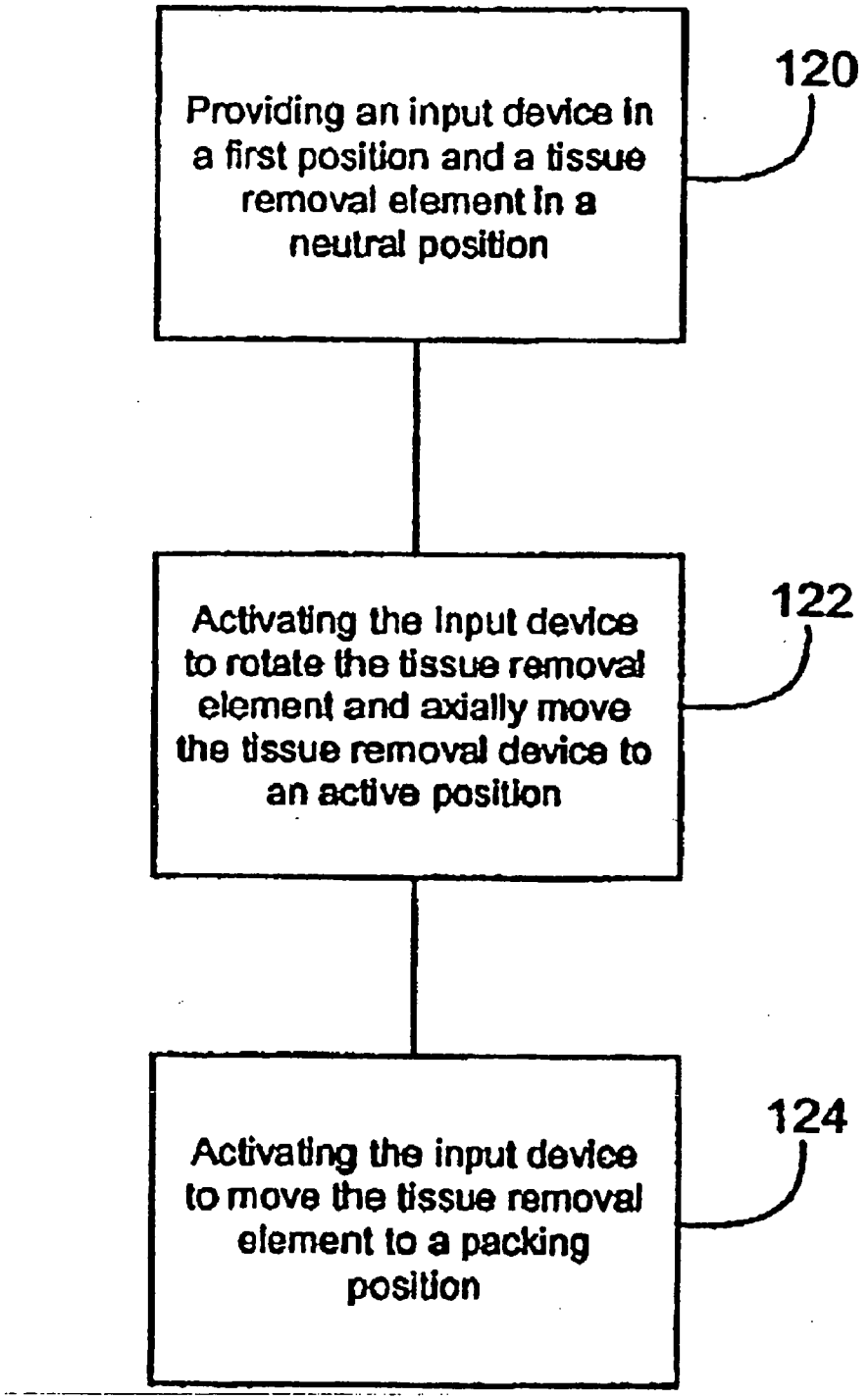

Providing an input device in a first position and a tissue removal element in a neutral position
120
Activating the input device to rotate the tissue removal element and axially move the tissue removal device to an active position
122
Activating the input device to move the tissue removal element to a packing position
124

FIG. 20

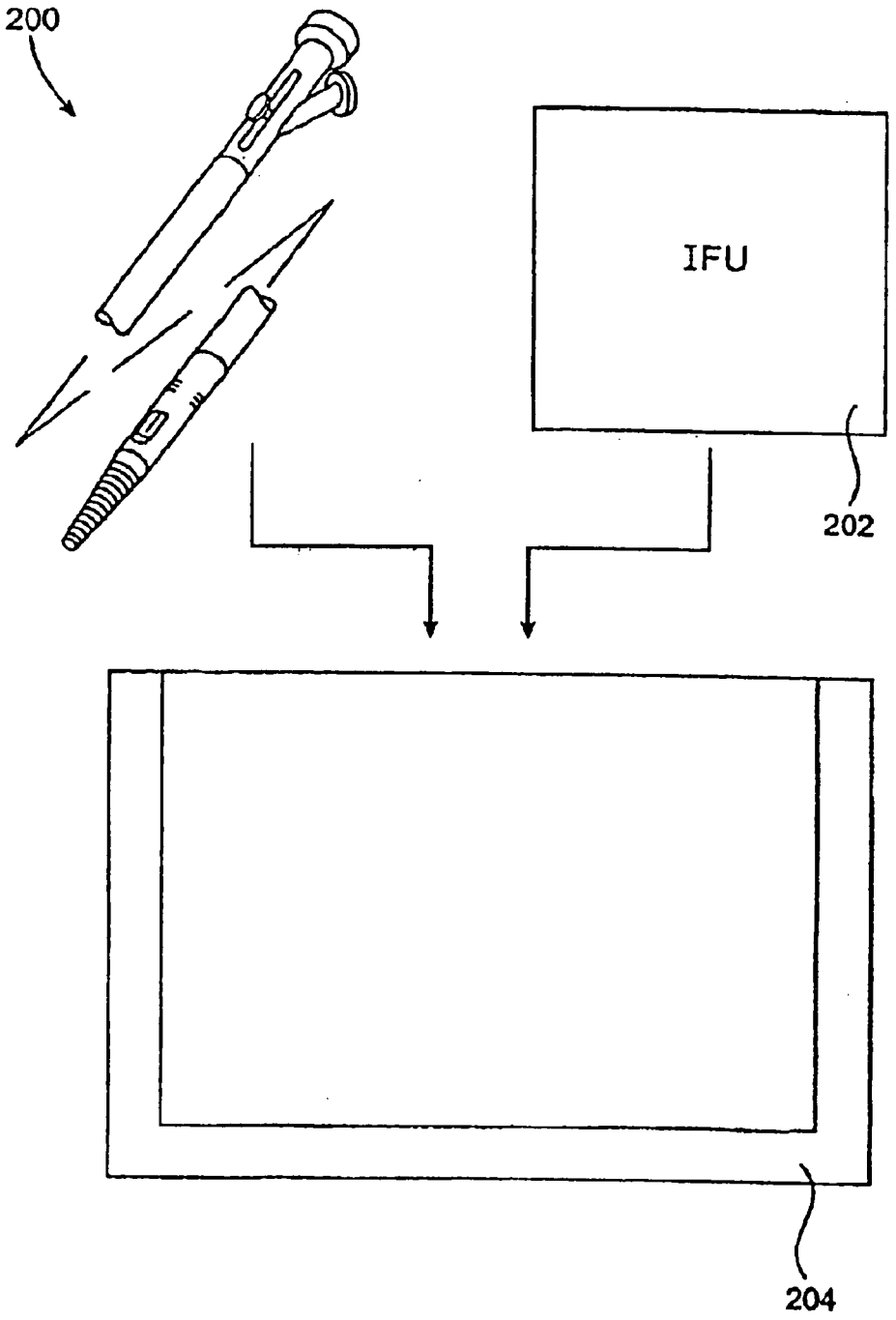


FIG. 21

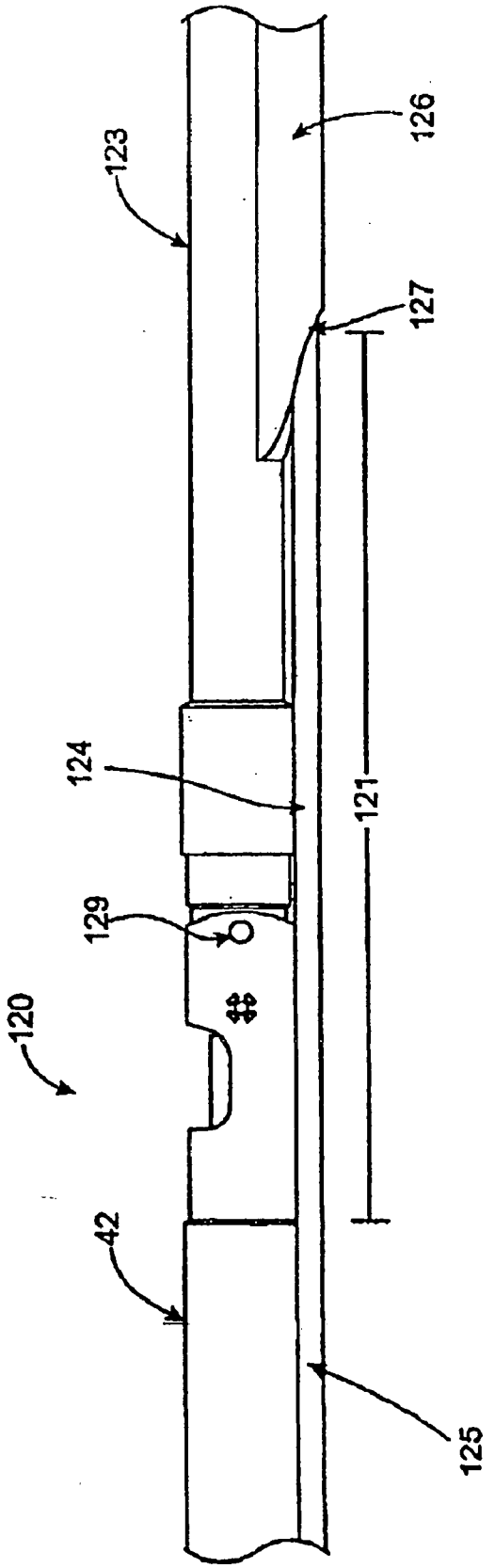


FIG. 22A

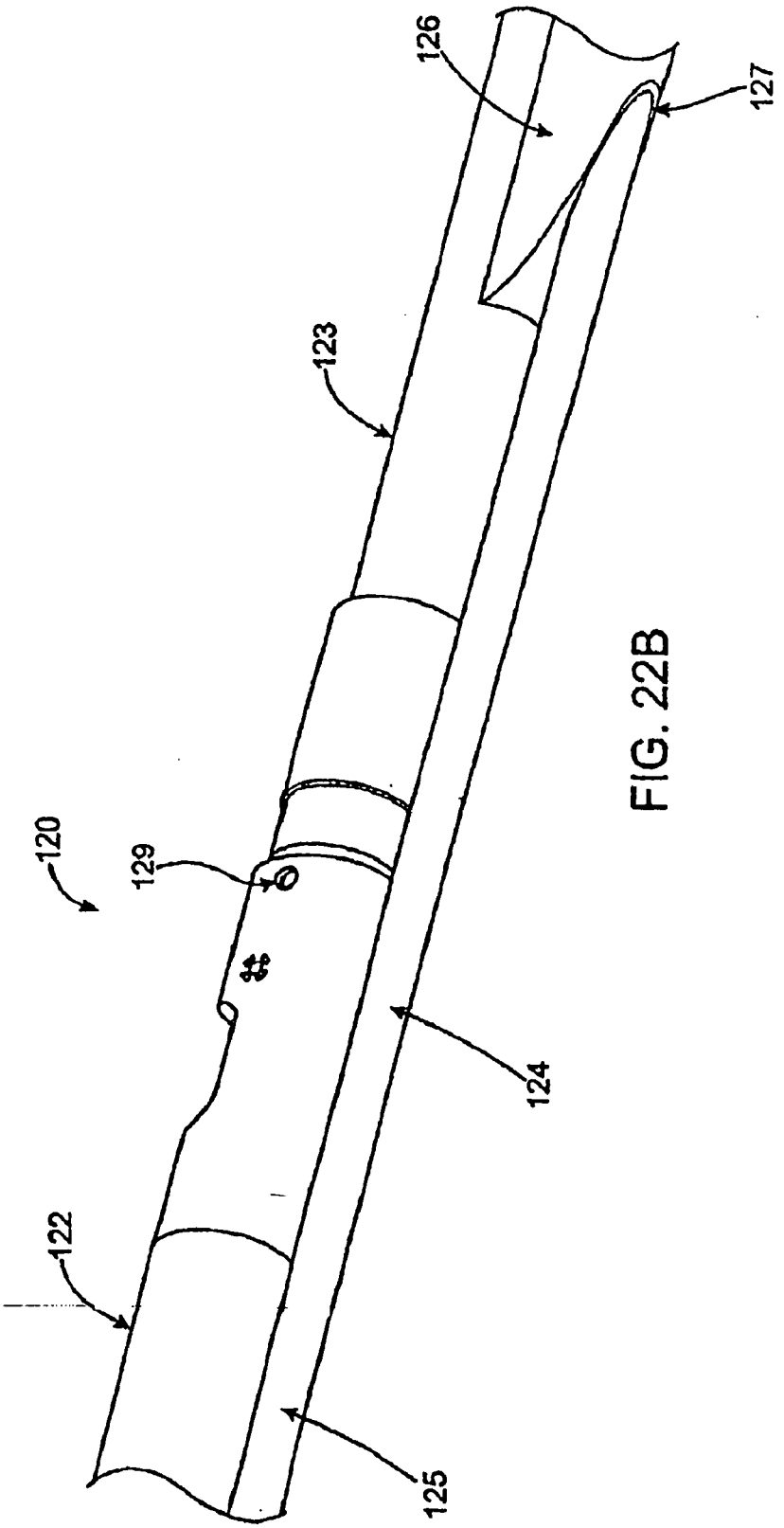


FIG. 22B

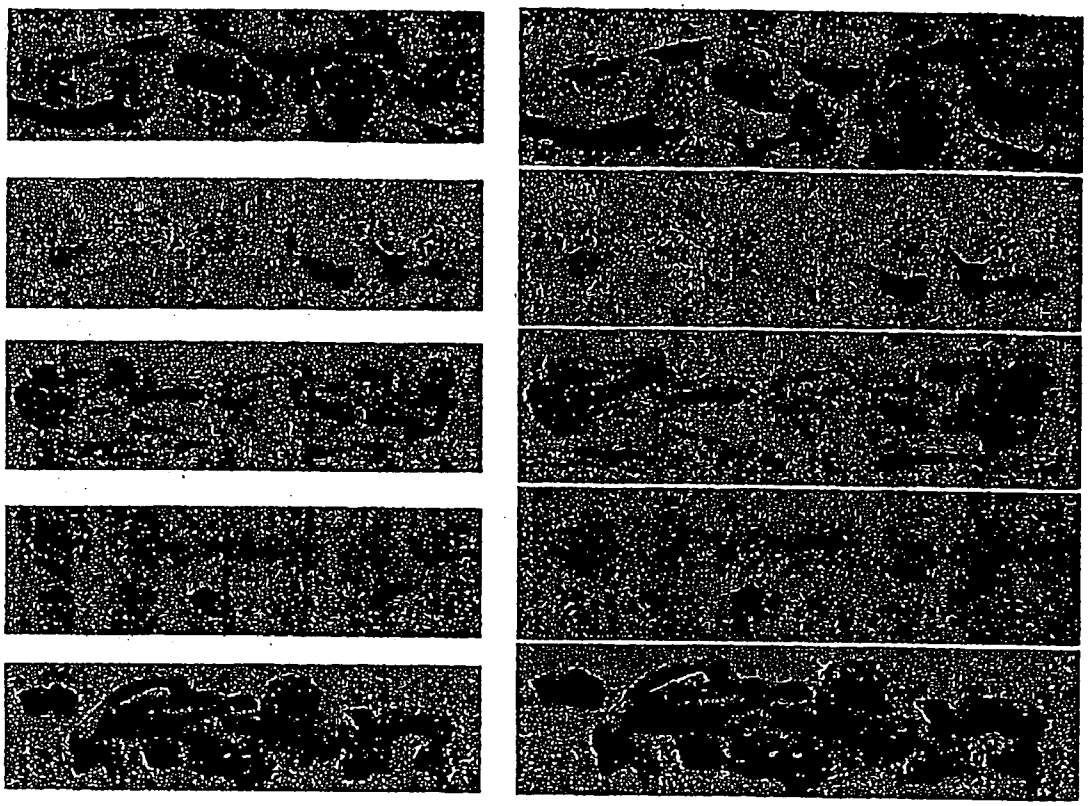


FIG. 23

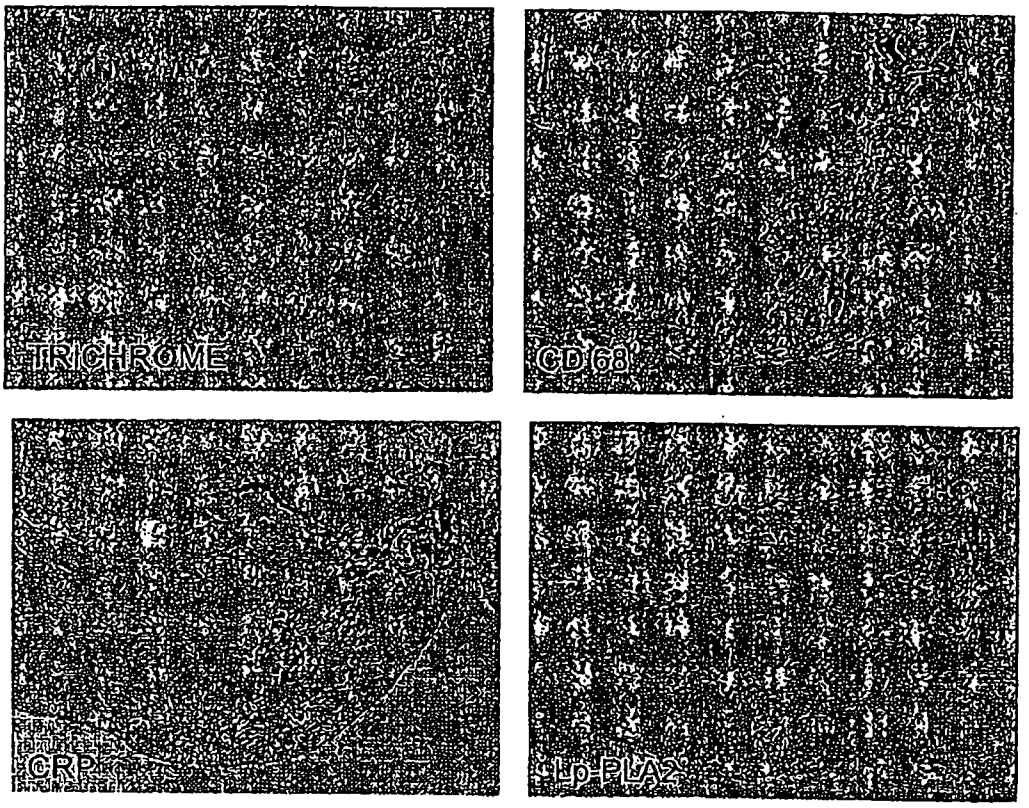


FIG. 24

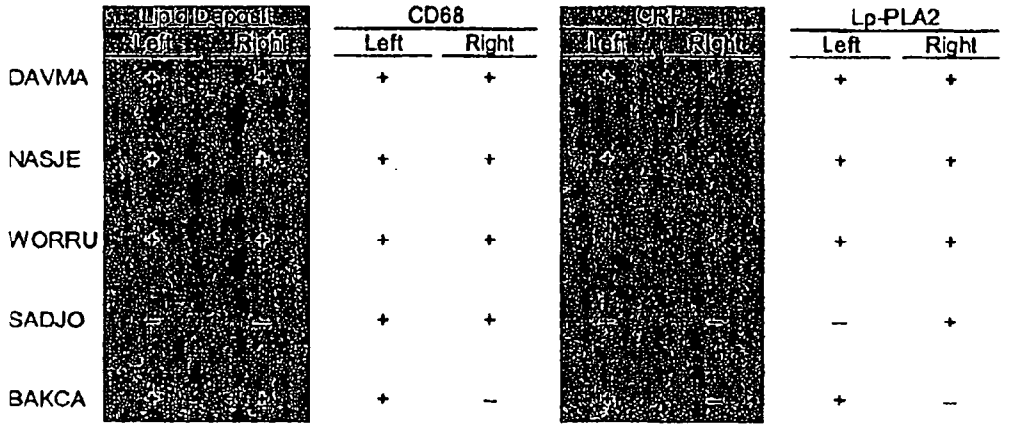

Lipid Deposit
Left
Right
CD68
Left
Right
CRP
Left
Right
Lp-PLA2
Left
Right
DAVMA
NASJE
WORRU
SADJO
BAKCA

FIG. 25

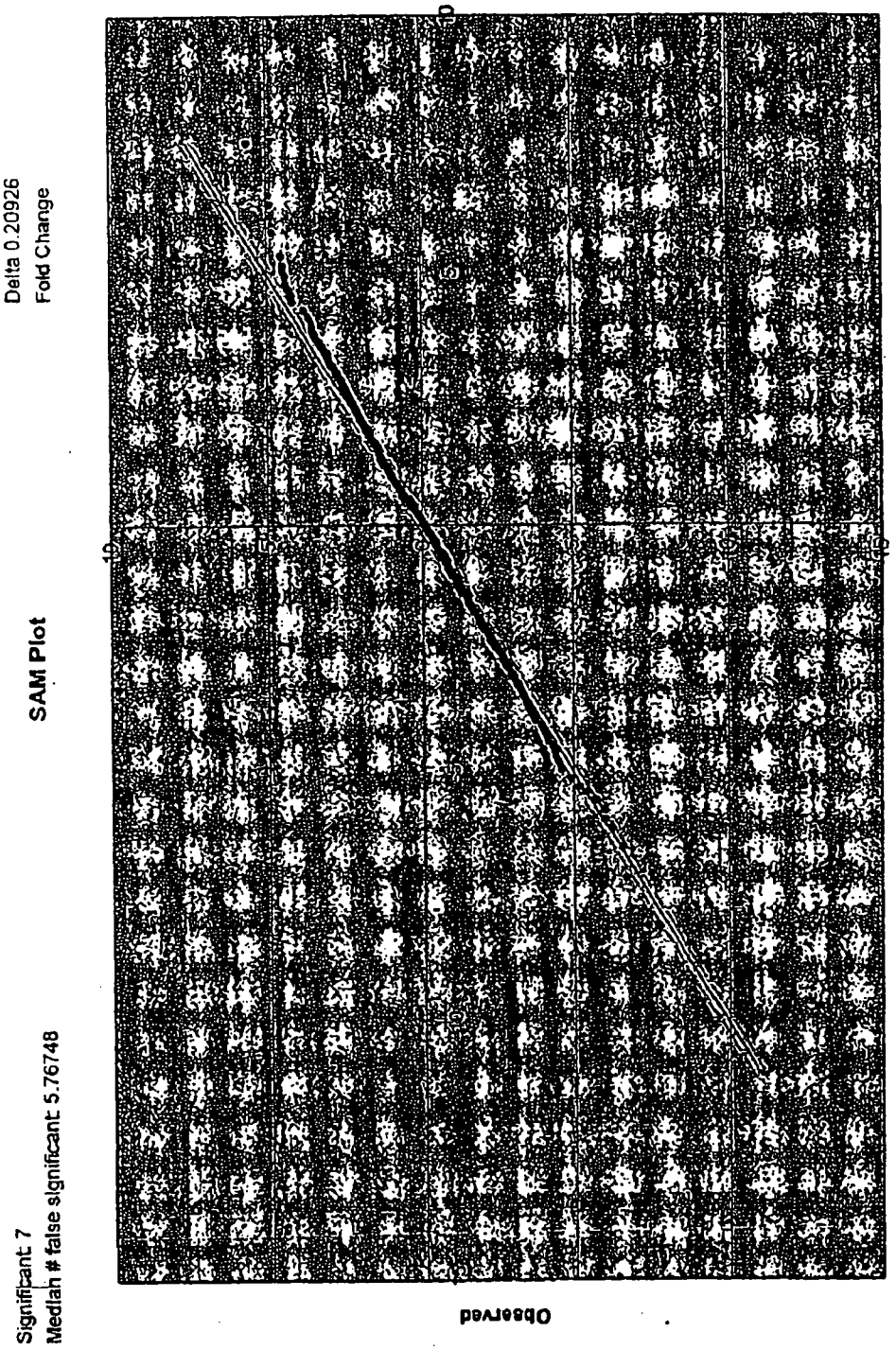

SAM Plot
Delta 0.20926
Fold Change
Significant: 7
Median # false significant: 5.76748
Observed
Expected

FIG. 26

METHOD OF EVALUATING A TREATMENT FOR VASCULAR DISEASE

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present application is a continuation-in-part of U.S. patent application Ser. No. 11/199,370 filed Aug. 9, 2005, which is a continuation in part of U.S. patent application Ser. No. 11/010,833 filed Dec. 13, 2004, entitled "Method of Evaluating Drug Efficacy for Treating Atherosclerosis" and Ser. No. 10/896,741, filed Jul. 21, 2004, entitled "Debulking Catheter and Methods", which is a continuation-in-part of U.S. patent application Ser. No. 10/288,559, filed Nov. 4, 2002, entitled "Debulking Catheter and Methods", which is a continuation-in-part of U.S. patent application Ser. No. 10/027,418, filed Dec. 19, 2001, entitled "Debulking Catheter", which claims the benefit of Provisional Patent Application Serial No. 60/257,704, filed Dec. 20, 2000, entitled "Debulking Catheter." U.S. patent application Ser. No. 10/288,559 further claims priority to Provisional Patent Application Serial No. 60/272,273 filed Feb. 27, 2001, entitled "Debulking Catheter" and Provisional Application No. 60/381,632, filed on May 17, 2002, entitled "Debulking Catheter", the complete disclosures of which are incorporated herein by reference.

[0002] The present application is also related to U.S. patent application Ser. Nos. 09/377,884, filed Aug. 19, 1999, entitled "Apparatus and Methods for Material Capture and Removal" and 09/377,894, filed Aug. 19, 1999, entitled "Apparatus and Methods for Removing Material From a Body Lumen," the complete disclosures of which are incorporated by reference.

BACKGROUND OF THE INVENTION

[0003] The present invention relates generally to percutaneous translumenal systems and methods for debulking body lumens. More particularly, the present invention relates to atherectomy catheters for excising atheroma and other materials from blood vessels and from stents. The present invention also relates to methods for the selective excision and testing of material from a body lumen, such as a blood vessel.

[0004] Cardiovascular disease frequently arises from the accumulation of atheromatous material on the inner walls of vascular lumens, particularly arterial lumens of the coronary and other vasculature, resulting in a condition known as atherosclerosis. Atherosclerosis occurs naturally as a result of aging, but may also be aggravated by factors such as diet, hypertension, heredity, vascular injury, and the like. Atheromatous and other vascular deposits restrict blood flow and can cause ischemia which, in acute cases, can result in myocardial infarction. Atheromatous deposits can have widely varying properties, with some deposits being relatively soft and others being fibrous and/or calcified. In the latter case, the deposits are frequently referred to as plaque.

[0005] One conventional treatment for cardiovascular disease is the use of stents. Endolumenal stents are commonly used to treat obstructed or weakened body lumens, such as blood vessels and other vascular lumens. Once deployed in the blood vessel, the stent can remain in the body lumen where it will maintain the patency of the lumen and/or support the walls of the lumen which surround it. One factor impeding the success of stent technology in endolumenal treatments is the frequent occurrence of in-stent restenosis, characterized by proliferation and migration of smooth muscle cells within and/or adjacent to the implanted stent, causing reclosure or blockage of the body lumen.

[0006] Atherosclerosis and restenosis can be treated in a variety of ways, including drugs, bypass surgery, and a variety of catheter-based approaches which rely on intravascular debulking or removal of the atheromatous or other material occluding a blood vessel. Of particular interest to the present invention, a variety of methods for cutting or dislodging material and removing such material from the blood vessel have been proposed, generally being referred to as atherectomy procedures. Atherectomy catheters intended to excise material from the blood vessel lumen generally employ a rotatable and/or axially translatable cutting blade which can be advanced into or past the occlusive material in order to cut and separate such material from the blood vessel lumen. In particular, side-cutting atherectomy catheters generally employ a housing having an aperture on one side, a blade which is rotated or translated by the aperture, and a balloon to urge the aperture against the material to be removed.

[0007] Although atherectomy catheters have proven very successful in treating many types of atherosclerosis and in-stent restenosis, improved atherectomy catheters and methods are continuously being pursued. For example, many currently available side-cutting atherectomy catheters have difficulty in capturing occluding material in the cutting aperture. To facilitate material capture, the cutting aperture is frequently elongated to increase the area into which the material can penetrate. Such elongation typically requires an equivalent lengthening of the cutter housing. Since most cutter housings are rigid, such lengthening makes it more difficult to introduce the distal end of the catheter through tortuous regions of the vasculature.

[0008] Another shortcoming of many currently available atherectomy catheters is that they typically require a balloon positioned opposite the cutting window to urge the cutting window into contact with occluding material. Such balloons, however, unduly increase the size of the distal portion of the catheter. Even with the balloon, the amount of material that can be removed by conventional atherectomy catheters is limited by the size of the cutting window. Other disadvantages of some catheters include cutting elements with less than ideal hardness, inadequate storage space within the catheter for containing removed material, sub-optimal guide wire lumens, and/or the like.

[0009] Furthermore, the currently available atherectomy catheters generally provide material insufficient in quantity and/or quality for testing by many histological, array, proteomic or other biochemical or molecular methods. For example, in one report a device and method collected less than about 50 mg of tissue. (Safian et al., *Circulation* 82:305-307 (1990)). This amount of material is not typically enough to carry out more than one test, or is insufficient to successfully carry out a number of diagnostic tests available to the physician or researcher.

[0010] Presently, the process of testing experimental drugs to treat atherosclerosis is complicated by the question: at what endpoint in the animal or patient is efficacy of the drug apparent? Historically the endpoint has been mortality, both

in laboratory animals, and human subjects. Mortality, while definitive, often takes years before solid conclusions regarding efficacy can be drawn. Mortality is also confounded by the fact that it is only useful if the cause of death is related to the atherosclerotic condition. It would be of great advantage to clinical research in the area of atherosclerosis if a new quicker method of determining an endpoint for drug studies could be developed.

[0011] For these reasons, it would be advantageous to have atherectomy catheters which could access small, tortuous regions of the vasculature and remove atheromatous and other occluding materials from within blood vessels and stents in a controlled fashion. In particular, it would be desirable to have atherectomy catheters which could facilitate capturing and invagination of atheromatous materials. Particularly, those capable of in vivo capturing and removing at least one contiguous tissue strand of sufficient quantity and quality for testing in vitro. Ideally, such catheters and methods for their use would be adaptable for use in a variety of body lumens, including but not limited to coronary and other arteries. It would further be desirable to be able to remove arterial plaque tissue from body lumens so as to be able to determine drug efficacy. At least some of these objectives will be met by the present invention.

BRIEF SUMMARY OF THE INVENTION

[0012] In one aspect, the invention provides a method of evaluating a treatment of a patient having vascular disease. A first sample of tissue is removed from a vascular lumen of the patient. At least one property of the tissue is analyzed. A treatment is administered to the patient. A second sample of tissue is removed from a vascular lumen of the patient. The at least one property is analyzed in the second sample. Properties of the first and second samples are compared to determine an effect of the treatment on the patient.

[0013] In another aspect of the invention a method is provided for evaluating an effect of a treatment on a patient having vascular disease. Tissue is removed from a site in a vascular lumen in a patient. A treatment is administered to the patient. The patient is monitored for recurrence of the tissue at the site in the vascular lumen. An effect of the treatment is identified if the vascular tissue does not recur at the site. This evaluation can be performed in a population of subjects and a reduction in recurrence rate in the population identifies a treatment with an effect on at least some members of the population.

[0014] In still another aspect of the invention a method is provided for determining if a test molecule localizes in tissue in a vascular lumen. A test molecule having a detectable tag is introduced into vasculature of a patient having vascular disease. A sample of tissue is removed from a vascular lumen of the patient. The presence and/or amount of the test molecule having the detectable tag in the tissue is determined.

[0015] Still another embodiment of the invention is a method of evaluating a treatment of a patient having vascular disease. An atherectomy catheter is introduced percutaneously in the patient and directed to a first site in a vascular lumen which contains tissue. A first sample of tissue is removed from the vascular lumen of the patient. At least one property of the tissue is analyzed. A treatment is administered to the patient. An atherectomy catheter is reintroduced percutaneously in the patient and directed to a second site in a vascular lumen which contains tissue. A second sample of tissue is removed from the second site of the patient. The at least one property is analyzed in the second sample. Properties of the first and second samples are compared to determine an effect of the treatment on the patient.

[0016] For a further understanding of the nature and advantages of the invention, reference should be made to the following description taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] **FIG. 1A** is a perspective view of a debulking catheter of the present invention.

[0018] **FIG. 1B** is a side view of a portion of a debulking catheter as in **FIG. 1A**, where the body has a rigid distal portion with a bend, according to one embodiment of the present invention.

[0019] **FIG. 2** is an exploded view of an exemplary distal portion of the debulking catheter of the present invention.

[0020] **FIG. 3A** is an end view of the distal portion of the debulking catheter of **FIG. 1A** in which the cutter is in a closed position in the catheter body.

[0021] **FIG. 3B** is a sectional view along Line A-A of **FIG. 3A**.

[0022] **FIGS. 3C and 3D** are views of the distal portion of a debulking catheter, where the distal portion has a locking shuttle mechanism.

[0023] **FIG. 4A** is an end view of the distal portion of the debulking catheter of **FIG. 1A** in which the cutter is in an open position outside of the cutting window.

[0024] **FIG. 4B** is a sectional view along Line A-A of **FIG. 4A**.

[0025] **FIGS. 4C and 4D** are views of the distal portion of a debulking catheter, where the distal portion has a locking shuttle mechanism.

[0026] **FIG. 5A** is an end view of the distal portion of the debulking catheter of **FIG. 1A** in which the cutter is in a packing position within a tip of the catheter.

[0027] **FIG. 5B** is a sectional view along Line A-A of **FIG. 5A**.

[0028] FIGS. **6** to **8** illustrate a monorail delivery system of the present invention.

[0029] **FIG. 9A** is a perspective view of a cutter of the present invention.

[0030] **FIG. 9B** is an end view of the cutter of **FIG. 9A**.

[0031] **FIG. 9C** is a sectional view of the cutter along Line A-A of the cutter of **FIGS. 9A and 9B**.

[0032] **FIG. 10A** is a perspective view of a in-stent restenosis cutter of the present invention.

[0033] **FIG. 10B** is an end view of the cutter of **FIG. 10A**.

[0034] **FIG. 10C** is a sectional view of the cutter along Line B-B of the cutter of **FIGS. 10A and 10B**.

[0035] **FIG. 11A** is a perspective view of another in-stent restenosis cutter of the present invention.

[0036] **FIG. 11B** is an end view of the cutter of **FIG. 11A**.

[0037] **FIG. 11C** is a sectional view of the cutter along Line C-C of the cutter of **FIGS. 11A and 11B**.

[0038] **FIG. 11D** is a side view of another embodiment of a cutter, shown partially within a catheter body.

[0039] **FIG. 12** illustrates a proximal handle and cutter driver of the present invention.

[0040] **FIG. 13** illustrates a cutter driver with a handle cover removed.

[0041] FIGS. **14** to **16** illustrate three positions of the lever for controlling the cutter.

[0042] **FIG. 17** is a simplified flow chart illustrating a method of the present invention.

[0043] **FIGS. 18 and 19** illustrate a method of the present invention.

[0044] **FIG. 20** schematically illustrates another method of the present invention.

[0045] **FIG. 21** illustrates a kit of the present invention.

[0046] **FIGS. 22A** and B illustrate some exemplary guidewire lumens of the present invention.

[0047] **FIG. 23** depicts the gross samples of plaque tissue removed from the left leg (left side of the figure) and the right leg (right side of the figure) of several patients.

[0048] **FIG. 24** depicts the histological staining of lipid deposit (trichrome), CD 68, CRP, and Lp-PLA2 in a single patient.

[0049] **FIG. 25** presents data from 5 patients indicating by positive staining in the left versus the right leg the presence "+" or absence of "−" Lipid deposit, CD68, CRP, and Lp-PLA2.

[0050] **FIG. 26** presents gene array data from plaque excised from the right and left legs of several patients.

DETAILED DESCRIPTION OF THE INVENTION

[0051] The catheters used in the methods of the present invention are designed to debulk atheroma and other occlusive material from diseased body lumens, and in particular coronary arteries, de novo lesions, and in-stent restenosis lesions. The catheters and methods, however, are also suitable for treating stenoses of body lumens and other hyperplastic and neoplastic conditions in other body lumens, such as the ureter, the biliary duct, respiratory passages, the pancreatic duct, the lymphatic duct, and the like. Neoplastic cell growth will often occur as a result of a tumor surrounding and intruding into a body lumen. Debulking of such material can thus be beneficial to maintain patency of the body lumen. The catheters and methods of the present invention also provide methods that provide lumenectomy samples or materials that are of higher quality and quantity that typically have been provided by prior devices. The material provided is typically a contiguous strip of tissue removed from the lumen interior wall that ranges from about 1 mg to about 2000 mg and wherein the tissue retains the structure of the tissue prior to removal. Advantageously, the contiguous strip or strand of tissue removed will typically have a length that is longer than a length of the cutting window. While the remaining discussion is directed at debulking and passing through atheromatous or thrombotic occlusive material in a coronary artery, it will be appreciated that the systems and methods of the present invention can be used to remove and/or pass through a variety of occlusive, stenotic, or hyperplastic material in a variety of other body lumens. For example, the ability to remove arterial plaque tissue from an appendage (e.g., leg or arm) in a sufficient amount and of a sufficient quality that the plaque tissue can be tested for one or more markers provides the opportunity to employ a method of testing drug efficacy in a clinical study for treating atherosclerosis.

[0052] Samples which are removed from a lumen, according to the invention, are lumenectomy samples. Typically these consist of vascular deposits. Deposits in vessel lumens may restrict blood flow and may cause ischemia, depending on their size, geometry, and properties. The vascular deposits in the lumen may be atheromas, which may be soft or fibrous or calcified. Calcified deposits are referred to as plaque. According to the invention one can remove all or a portion of a vascular deposit in a particular site. Multiple sites can be used as a source of test material, or multiple samples can be obtained from the same site at multiple times. If multiple time samplings are used, the effects of various treatments between the samplings can be observed. Alternatively, samples can be taken at various times without treatments merely to monitor general disease state of the vasculature. The vasculature from which a sample may be removed includes peripheral vasculature, coronary vasculature, and arteries.

[0053] Treatments which may be evaluated using the removed vascular deposits of the present invention include administration of pharmaceutical, chemical, or biological agents, as well as treatments with devices. The agents may have known pharmacological activities or may be previously unknown to have such activities. The agents may be delivered systemically or locally. Devices may, for example, administer energy in various forms to a body. Typically this will be from an external energy source. Examples of treatments with such devices include administration of radiation, laser, sonar, etc. Other prosthetic devices which exert mechanical actions on a vessel, such as stents and balloons, can be used to treat vasculature as well. Typical agents which can be tested include, without limitation, plaque-reducing agents, anti-inflammatory agents, enzyme inhibitors, protein synthesis inhibitors, inhibitors of cell proliferation, transcription factor inhibitors, lipid transport molecules, cholesterol-reducing agents, thrombolytic molecules, signal inhibitors, anti-platelet molecules, kinase inhibitors, and statin drugs. Combinations of agents can be evaluated, as well as combinations of treatments, and combinations of one or more agents and one or more treatments.

[0054] Properties of the removed lumenectomy samples are determined using known methods and protocols for examining tissue samples. These include, without limitation, the presence of a marker, the level of a marker, a modification of a marker, the activity of a protein, the activity of an RNA, transcription (e.g., capacity or level), translation (e.g., capacity or level), ligand binding, cellular activity, proliferation (e.g., capacity or index), inflammation, and

infection. Markers which are analyzed may be, without limitation, nucleic acid markers or protein markers. Examples of markers which may be analyzed or determined are growth factors, growth factor receptors, apoptotic markers, cell-cycle proteins, transcriptional regulators, proliferative markers, adhesion molecules, cytokines, chemokines, chemokine receptors, coagulation factors, fibrinolytic markers, oxidative stress related molecules, and extracellular matrix markers. Markers can include peptides or polypeptide markers as well as protein markers.

[0055] Treatments can be evaluated for their effect on vascular disease by looking for changes in the properties of lumenectomy material. As mentioned above, such changes can be evaluated at one or more sites in the body. Alternatively, a particular site which has been subjected to a lumenectomy can be monitored at one or more time points to determine whether vascular deposits are recurring at the site of the lumenectomy. Typically such monitoring can be performed with an imaging technique. These techniques include without limitation sonography, radiography, magnetic resonance imaging, angiography, and fluoroscopy. However, additional lumenectomy procedures can also be done to determine if vascular deposits have recurred.

[0056] According to another embodiment a test molecule is evaluated to determine whether it localizes to vascular deposits in lumens. Molecules which do so localize can be used diagnostically in combination with imaging techniques to identify and/or monitor vascular deposits. Test molecules will be tagged with a detectable moiety. Such moieties may be any that is convenient for a particular technique. Examples of detectable tags include but are not limited to radioactive moieties, fluorescent moieties, antibodies, labeled antibodies, ligands, and enzymes. Each of these are typically used with various techniques to readily detect, for example, products of reactions or biological pathways. Any such moiety can be selected as is appropriate for the detection means to be used. Means of labeling test molecules with tag moieties are also well known in the art and can be selected by the skilled artisan.

[0057] The present invention provides methods for in vivo excision and removal of material from an inner wall of one or more body lumens that is of higher quantity and quality than prior devices or methods. The material removed therefore is better suited for use in various testing methods. Particularly, the methods provide sufficient material of better quality and quantity for use in one or more tests from a single percutaneous translumenal lumenectomy procedure. Further, the material typically maintains the structure possessed by the material in vivo. This provides for the ability to carry out certain tests, such as histology, cytopathology, and other tests that have been difficult to perform using prior devices and methods.

[0058] In one embodiment, the method of excising and testing material from a body lumen comprises providing a catheter having a rotating cutter, a collection chamber, and a cutting window, the rotating cutter being movable between a stored position and an exposed position, at least part of the rotating cutter becoming exposed through the cutting window when moving the cutter to the exposed position. The catheter is advanced translumenally through the body lumen to move or plane the rotating cutter through material in a first site in the body lumen, the rotating cutter remaining in the exposed position so that the cutter and the window maintain their orientation with respect to one another when advancing the catheter and planing through the material. The planing action of the present invention provides a substantially consistent and even tissue removal through the body lumen. The contiguous strand of material cut by the rotating cutter is directed through the cutting window and into the collection chamber as the catheter is advanced through the material. The material can then be removed from the collection chamber and one or more tests performed on at least a portion of the material removed from the collection chamber.

[0059] The material excised from the body lumen will vary in length and will depend on the catheter configuration, the type of material removed, the body lumen, and the like. However, in certain embodiments, the material will be in the form of contiguous strands that have a substantially consistent depth and width of tissue cuts. The material is typically longer than the length of the cutting window (but it may be shorter), and typically has a length of about 2.0 mm or longer, and sometimes between about 0.5 cm up to about 10 cm or longer in length. Advantageously, the planing action of the catheter provides a material tissue structure that reflects the actual in vivo tissue structure, and provides information about larger portions of the disease state of the body lumen.

[0060] Tissue retrieved via the present invention provides an opportunity for greater confidence in test results for single or multiple tests due to reduced sampling errors resulting from greater tissue volume and enhanced tissue quality than was previously possible. Previously, the retrieved atherectomized tissue samples had problems because there was only angiographic control possible for the evaluation of how much stenotic tissue has been sampled. With the present invention, it is more confidently known how much stenotic tissue is sampled with a retrieval. Generally, the smooth muscle cells of the stenotic material show a range of phenotypes, but most of the cells contained myofilaments as well as a relatively high amount of synthetic organelles, such as rough endoplasmic reticulum, Golgi apparatus and mitochondria. A larger tissue sample of better quality and more confidence in the retrieval location can help determine with confidence how much stenotic tissue is retrieved in the procedure. Because the absence of inflammatory cells in excised tissue may be only one of many variables in sorting out a cardiovascular condition, the presence of the inflammatory cells within critical areas of plaque may be more important than their sheer number. Using the methods of the present invention, the location and degree of inflammatory cells present may be determined in order to facilitate a more informed diagnosis.

[0061] In the past, there has been difficulty obtaining sufficient plaque material to perform proliferation studies and to sub-cultivate tissue. The problem associated with the inability to obtain fresh human plaque tissue is underscored by the significant need for a tissue model wherein smooth muscle cells can be analyzed with as many of the original characteristics attributed to the previous in vivo injury as possible. Sufficient tissue of good quality will obviate the need to cultivate these cells. To date it has not been possible to directly compare smooth muscle cells from restenotic and

primary lesions, a comparison that could be facilitated using primary and restenotic tissue retrieved by the present invention.

[0062] The material removed from the collection chamber, or a portion thereof, can be placed in a preserving agent, a tissue fixative, and or a preparation agent suitable for a desired test prior to testing the material. The material removed from the patient by this method is typically at least one or more contiguous strip(s) of material that maintains the structure of the material in vivo. The quantity of material removed by the method can be from about 1 mg to about 2000 mg. Typically the amount of material is about 1 mg to about 100 mg, about 100 mg to about 200 mg, about 200 mg to about 300 mg, 300 mg to about 400 mg, 400 mg to about 500 mg, 500 mg to about 600 mg, about 600 mg to about 700 mg, 700 mg to about 800 mg, or about 800 mg to about 2000 mg. In a typical procedure about 400 mg to about 600 mg of material is removed and available for testing and/or storage. A preferred embodiment of the present invention provides for the collection of one or more contiguous strips of material from the inner surface of the body lumen that is longer than a largest dimension of the cutting window. In a particular example, the material can comprise plaque tissue.

[0063] The methods of the present invention provide high quality material in a sufficient quantity that allows for multiple testing methods (e.g., validation testing, repeat testing, etc.) and provides a sufficient amount of sample to allow storage of an amount of sample to allow later confirmatory or additional testing to confirm a diagnosis without having to subject the patient to another percutaneous translumenal lumenectomy procedure. The methods can provide sufficient high quality material for tests comprising genomic screening, DNA hybridization, RNA hybridization, gene expression analysis, PCR amplification, proteomic testing, drug efficacy screening, a presence of one or more protein markers, a presence of one or more DNA markers, a presence of one or more RNA markers, histological testing, histopathology, cytopathology, cell and tissue type analysis, biopsy, and the like. Additionally, the material can also be cultured to determine reactivity to drugs, e.g., therapeutic drugs, and the like. Being able to carry out such testing provides for the ability to perform one or more tests comprising, for example, but not limited to, analyzing the material for the presence of DNA, RNA, or a protein marker comprising a smooth muscle proliferative promoter, a smooth muscle proliferative inhibitor, a cellular marker, an apoptotic marker, a cell cycle protein, a transcriptional factor, a proliferative marker, an endothelial growth factor, an adhesion molecule, a cytokine, a chemokine, a chemokine receptor, an inflammation marker, a coagulation factor, a fibrinolytic factor, an oxidative stress related molecule, an extracellular matrix molecule, an interleukin, a growth factor, a glycoprotein, a proteoglycan, a cell-surface marker, a serum marker, and or an immune factor, and the like. Tests for each of these molecules and others are well known to the skilled artisan as are methods and preservatives, fixatives and preparation agents for adding to all or a portion of the material collected.

[0064] In another embodiment of the present invention the method can further comprise moving the cutter to the stored position and repositioning the catheter at a second site. The cutter is exposed by moving the cutter to the exposed position and the catheter is advanced to move the rotating cutter through material in the second site, the rotating cutter remaining in the exposed position so that the cutter and the window maintain their orientation with respect to one another when advancing the catheter through the material. The material cut by the rotating cutter is directed through the cutting window and into the collection chamber as the catheter is advanced through the material. The first and second sites can be in either the same or a different body lumen.

[0065] Another embodiment of the methods of the present invention for removing material from a vascular location comprises the steps of providing a catheter having a body, an opening leading to a collection chamber, and a cutter, the cutter being movable between a stored position and an exposed position, the cutter becoming at least partially exposed when moving from the stored position to the exposed position. The catheter is then percutaneously introduced into and translumenally advanced through a patient's vascular system with the cutter in the stored position, the catheter being introduced into the vascular location where material is to be removed. The cutter is then exposed by moving the cutter to the exposed position and the cutter is rotated. The catheter is then advanced after the exposing step and during the rotating step, wherein the rotating cutter and the opening advance together so that material cut by the rotating cutter is directed through the opening and into the collection chamber as the catheter is advanced. Subsequent to excision of the material, the catheter is removed from the vascular location and the material collected in the collection chamber is harvested and one or more tests are carried out on at least a portion of the material removed from the collection chamber.

[0066] The material removed from the collection chamber, or a portion thereof, can be placed in a preserving agent, a tissue fixative, and or a preparation agent suitable for a desired test prior to testing the material. The material removed from the patient by this method is typically at least one or more contiguous strip(s) of material that maintains the structure of the material in vivo. The quantity of material removed by the method can be from about 1 mg to about 2000 mg. Typically the amount of material is about 1 mg to about 100 mg, about 100 mg to about 200 mg, about 200 mg to about 300 mg, 300 mg to about 400 mg, 400 mg to about 500 mg, 500 mg to about 600 mg, about 600 mg to about 700 mg, 700 mg to about 800 mg, or about 800 mg to about 2000 mg. In a typical procedure about 400 mg to about 600 mg of material is removed and available for testing and/or storage. A preferred embodiment of the present invention provides for the collection of one or more contiguous strips of material from the inner surface of the lumen that is longer than a largest dimension of the cutting window. In a particular example, the material can comprise plaque tissue. The material can be collected from a single site or at least one additional site in the same or a different body lumen.

[0067] The material produced by the methods of the invention provide a lumenectomy composition comprising at least one contiguous tissue stand collected in vivo from an inner surface of the body lumen of a subject. In one embodiment the body lumen can be an artery or other lumen or vessel of the circulatory system and the material can comprise arterial plaque and associated tissue. The contiguous stand of tissue provided by the disclosed methods provide a sufficient amount of high quality material to

successfully perform at least one or more tests comprising, for example, genomic screening, DNA hybridization, RNA hybridization, gene expression analysis (including serial analysis of gene expression), PCR amplification, proteomic testing, drug efficacy screening, a determination of the presence of one or more protein markers, a determination of the presence of one or more nucleic acid markers, a determination of the presence of one or more RNA markers, histological testing, histopathology, cytopathology, cell type analysis, tissue type analysis, biopsy, and the like. Methods for performing each of the tests are well known to the skilled artisan. It is also well known that material collected from a patient can be added to a preserving agent, tissue fixative, or a preparation agent in order to prepare at least a portion of collected material for the desired test. Agents known in the art for preserving, fixing or preparing the material for later use include, for example, saline, heparinized saline, liquid nitrogen, formalin, a membrane lysis agent, a RNA or DNA preparation agent, and the like. Particular tests that can be carried our successfully on the excised lumenectomy material removed by the methods of the present invention include, but are not limited to, histology techniques including hematoxylin and eosin staining, connective tissue staining, carbohydrate staining, and lipid staining, and the like. In addition, tissue array testing, enzyme histochemistry, transmission electron microscopy, immunohistology, immunocytochemistry, immunoassays, immunofluorescent assays, immunoprecipitation assays, ELISA, flow cytometry, fluorescent activated cell sorting, radioimmunochemistry, electrophoresis, two-dimensional gel electrophoresis, Western blotting, protein sequencing, mass spectrometry, proteomic analysis, and protein microarray analysis can be carried out. Further, cytogenetic testing, Northern blotting, RNase protection assays, in situ hybridization assays, DNA microarray testing, reverse transcription polymerase chain reaction PCR (RT-PCR), Southern blotting, DNA sequencing, PCR amplification, single strand conformational polymorphism assays, single strand polymorphism (SNP) assays, and serial analysis of gene expression (SAGE) assays, can be successfully carried out with the lumenectomy material compositions collected by the methods and devices disclosed herein. The compositions of the present invention or portions thereof can also be prepared for storage for later testing.

[0068] In certain embodiments of the present invention the material collected can be analyzed for the presence of DNA, RNA, or protein markers comprising smooth muscle proliferative promoters (platelet-derived growth factor (PDGF), and PDGF receptor), basic fibroblast growth factor (FGF) and FGF receptor, interleukin 1 (IL-1), or transforming growth factor α (TGFα), and the like, smooth muscle proliferative inhibitors (nitric oxide/endothelial-derived relaxing factors (NO/EDRF), interferon γ (IFγ), transforming growth factor β (TGFβ), or TGFβ receptor, and the like), cellular markers (including CD68, CD3, CD4, CD8, CD20, smooth muscle actin, or CD31, and the like), apoptotic markers (Bcl-x, Bcl-2, Bax, Bak, or P53, and the like), cell cycle proteins (cyclin A, cyclin B, cyclin D, or cyclin E, and the like), transcriptional factors (transcription factor NFκB, transcription factor E2F, transcription factor CREB, or transcription factor KLF5/BTEB2, and the like), proliferative markers (Ki-67 or proliferating cell nuclear antigen (PCNA), and the like), endothelial growth factors (vascular endothelial growth factor (VEGF), and the like), adhesion molecules (intercellular adhesion molecule-1 (ICAM-1), CD11a/CD18 (LFA-1), CD11b/CD18 (MAC-1), vascular cell adhesion molecule-1 (VCAM-1), β-selectin (CD62P), or integrin, and the like), cytokines (interleukin 6 (IL-6) or interleukin 8 (IL-8), and the like), chemokines and chemokine receptors (monocyte chemoattractant protein 1 (MCP-1) and its receptor CCR2, CX3C chemokine fractalkine and its receptor CX3CR1, or eotaxin and its receptor CCR3, and the like), inflammation markers (C-reactive protein, myeloperoxidase, or complement proteins, and the like), coagulation factors and fibrinolytic factors (fibrinogen, prothrombinogen, plasminogen activator, tissue factor, or glycoprotein receptor on platelets (GpIIb-IIIa), and the like), oxidative stress related molecules (oxidized LDL and its receptor CD36, or lipoxygenase, and the like), extracellular matrix molecules (collagen, matrix metalloproteinase (MMP), FK506-binding protein 12 (FKBP12), endothelial differentiation gene receptors (EDG receptors), ephrins, elastin, lamin receptor, monocyte colony stimulating factor (M-CSF), tumor necrosis factor (TNF), or PDZ domain proteins, and the like), interleukins (interleukin 1 (IL-1), interleukin 6 (IL-6), or interleukin 8 (IL-8), and the like), growth factors (platelet-derived growth factor (PDGF), basic fibroblast growth factor (FGF), transforming growth factor α (TGFα), or transforming growth factor β (TGFβ), and the like), glycoproteins, proteoglycans (versican, hyluronan, biglycan, or deorin, and the like), cell-surface markers, serum markers, and/or immune factors (stromal cell-derived factor 1a (SDF-1)), and the like). Other markers that can be sought include: interleukin-18, RANTES, fractalkine, interleukin-1-beta, matrix metalloproteinase-9, tumor necrosis factor-alpha, monocyte inflammatory protein alpha, E-selectin and P-selectin. Analysis of the excised material by any of the above tests can be used for diagnosis of a condition in a patient, design a treatment directive or protocol for a subject, monitor progress of a treatment regimen, or if tests from a number of individuals are compared, the information can be used in a multi-patient analysis, such as a cardiovascular disease population study.

[0069] In another aspect, the method of invention may be used to excise arterial plaque tissue from a vessel in an appendage in sufficient quantities and quality that at least one marker can be tested from the tissue. In preferred embodiments, at least part of the methods are carried out using the catheters of the present invention, but it should be appreciated that such methods may be carried out using any device capable of excising tissue from an appendage.

[0070] In one embodiment of evaluating the efficacy of a test pharmaceutical agent or biological agent in a patient having tissue within the lumen, e.g., arterial plaque burden. A first tissue sample, such as plaque tissue, can be removed from a first site, e.g., in an appendage of the patient. The tissue removed should be of a quantity and quality so as to be properly analyzed for at least one marker by one or more established method for detecting that marker. A test pharmaceutical agent or biological agent may then be administered to the patient for a period of time sufficient to show a measurable and significant change in the production of the marker being monitored. The appropriate test period of time may vary depending upon many factors including the expected efficacy of the test agent, the expected response time of the markers being looked at, the condition of the test population and perhaps other factors peculiar to other elements or indicia in the test design. The test period will probably be in a range from about one week to about one or

two years, but could be any appropriate length of time given the test agent and the test protocol.

[0071] After the test period of time is complete, a second sample can be removed from a second site, e.g., a second appendage of the patient. The tissue removed from the second site or appendage is also analyzed for its marker content in the same manner as the first tissue sample. The first and second appendages can be legs, but could also be arms. If the first appendage is an arm, the second appendage can be the opposing arm. Similarly, if the first appendage is a leg, the second appendage can be the opposing leg.

[0072] After the second tissue sample is analyzed for the marker content, the marker levels of the two samples are compared. The marker levels in the second plaque tissue sample could go up or down compared to the marker level of the first plaque tissue sample. The efficacy of the test pharmaceutical agent or biological agent to treat the condition could be indicated if a bad marker went down or a good marker went up. A bad marker is a marker that is presumed to indicate a worsening of the atherosclerosis in the patient. A good marker is a marker that is presumed to indicate an improvement of the atherosclerosis in the patient. If desired, one or more markers can be tested in the protocol. It follows also that both good and bad markers can be tested in a single protocol.

[0073] After the first level of the marker is compared with the second level of the marker to determine whether the test drug is efficacious in treating atherosclerosis in the patient, a determination can also be made about the dosage of the test pharmaceutical agent or biological agent. For example, perhaps the dosage should be increased or administered in a pattern over time, or reduced.

[0074] The test pharmaceutical agent or biological agent can be any test agent clinically acceptable for testing in humans or animals in an effort to treat artherosclerosis. A pharmaceutical agent may be any drug. A drug is a molecule that modifies an environment in the body. A biological agent may be any biologically active molecule, also having the potential to act as a drug in the body, but the activity of a biological agent is a biological activity such as, for example an ability to bind to another molecule that it contacts. Biological agents can be, for example, proteins, or parts of proteins, peptides, polypeptides, nucleic acids, lipids, fatty acids, or other molecules having an origin in molecules found within the body. The test agent (pharmaceutical or biological) will be considered a candidate for the clinical study if it is believed that it can reduce the arterial plaque or other tissue burden of the patient or reduce a marker associated with arterial plaque, or increase a marker associated with a reduction of arterial plaque. Examples of clinical test pharmaceutical agent or biological agents that could be tested in the method of the invention include but are not limited to: blood thinners, drugs that reduce inflammation, drugs that stimulate growth of new blood vessels, a combination of known atherosclerosis drugs, a combination of new drugs, a combination of an old and a new drug, gene-based drugs that modulate the expression of particular target genes in an inflammation or atherosclerosis gene pathway, a drug that lowers the level of triglycerides in a patient, a drug that raises the high density lipoprotein (HDL) levels in a patient, a drug that lowers the blood pressure of the patient, a vasoactive hormone, a drug that blocks lipoprotein-associated phospholipase A_2 enzyme activity, a drug that blocks the activity of an enzyme associated with atherosclerosis, a gene-based drug that modulates gene activity in an atherosclerotic condition, a vitamin, a nutritional supplement, a cholesterol reducing drug, a drug that reduces calcification in the body, a vasodilator, a drug administered in combination with stent therapy, a beta adrenergic blocker, a platelet inhibitor, an acetyl choline enzyme (ACE) inhibitor, a modulator of genes that are involved in plaque initiation, a modulator of genes that are involved in plaque progression, a test agent that modulates a metabolic pathway in atherosclerosis, high density lipoprotein (HDL), a drug that keeps cholesterol from sticking to arterial walls, a drug that inhibits acyl-CoA cholesterol acyl-transferase, a drug that raises HDL levels, and a drug that lowers LDL levels.

[0075] In addition, and not by limitation but only by example, a test pharmaceutical agent or biological agent of the invention can be an anti-inflammatory agent, an enzyme inhibitor, a protein inhibitor, an inhibitor of cell-proliferation, a transcription factor inhibitor, a lipid transport molecule, a cholesterol target, a thrombolytic, a biomarker target, a signal inhibitor, and an anti-platelet.

[0076] The present invention also provides methods of formulating a metabolic pathway in atherosclerosis. The method comprises introducing a marker having a tag into the patient having atherosclerosis. Arterial plaque tissue is then removed from a first appendage in the patient. The removed plaque tissue is analyzed by a method appropriate to an analysis of the marker with the tag for an activity of the marker having the tag. For example the marker may be an enzyme that is convertible to an active state in vivo. Once the presence of the marker activity is confirmed, the patient is administered a modulator of the activity of the marker. After a period of time deemed sufficient to allow the modulator to take effect has passed, arterial plaque tissue is removed from a second appendage of the patient. The marker with the tag is analyzed for the modulation of activity expected by the effects of the administered test modulating agent. A comparison is made between the activity of the tagged marker studied in the first sample with the activity of the tagged marker in the second sample to formulate an understanding about a metabolic pathway in atherosclerosis.

[0077] Apparatus for carrying out the methods described herein will generally comprise catheters having catheter bodies adapted for intralumenal introduction to the target body lumen. The dimensions and other physical characteristics of the catheter bodies will vary significantly depending on the body lumen which is to be accessed. In the exemplary case of atherectomy catheters intended for intravascular introduction, the proximal portions of the catheter bodies will typically be very flexible and suitable for introduction over a guidewire to a target site within the vasculature. In particular, catheters can be intended for "over-the-wire" introduction when a guidewire channel extends fully through the catheter body or for "rapid exchange" introduction where the guidewire channel extends only through a distal portion of the catheter body. In other cases, it may be possible to provide a fixed or integral coil tip or guidewire tip on the distal portion of the catheter or even dispense with the guidewire entirely. For convenience of illustration,

guidewires will not be shown in all embodiments, but it should be appreciated that they can be incorporated into any of these embodiments.

[0078] Catheter bodies intended for intravascular introduction will typically have a length in the range from 50 cm to 200 cm and an outer diameter in the range from 1 French to 12 French (0.33 mm: 1 French), usually from 3 French to 9 French. In the case of coronary catheters, the length is typically in the range from 125 cm to 200 cm, the diameter is preferably below 8 French, more preferably below 7 French, and most preferably in the range from 2 French to 7 French. Catheter bodies will typically be composed of an organic polymer which is fabricated by conventional extrusion techniques. Suitable polymers include polyvinylchloride, polyurethanes, polyesters, polytetrafluoroethylenes (PTFE), silicone rubbers, natural rubbers, and the like. Optionally, the catheter body may be reinforced with braid, helical wires, coils, axial filaments, or the like, in order to increase rotational strength, column strength, toughness, pushability, and the like. Suitable catheter bodies may be formed by extrusion, with one or more channels being provided when desired. The catheter diameter can be modified by heat expansion and shrinkage using conventional techniques. The resulting catheters will thus be suitable for introduction to the vascular system, often the coronary arteries, by conventional techniques.

[0079] The distal portion of the catheters of the present invention may have a wide variety of forms and structures. In many embodiments, a distal portion of the catheter is more rigid than a proximal portion, but in other embodiments the distal portion may be equally as flexible as the proximal portion. One aspect of the present invention provides catheters having a distal portion with a reduced rigid length. The reduced rigid length can allow the catheters to access and treat tortuous vessels and small diameter body lumens. In most embodiments a rigid distal portion or housing of the catheter body will have a diameter that generally matches the proximal portion of the catheter body, however, in other embodiments, the distal portion may be larger or smaller than the flexible portion of the catheter.

[0080] A rigid distal portion of a catheter body can be formed from materials which are rigid or which have very low flexibilities, such as metals, hard plastics, composite materials, NiTi, steel with a coating such as titanium nitride, tantalum, ME-92®, diamonds, or the like. Most usually, the distal end of the catheter body will be formed from stainless steel or platinum/iridium. The length of the rigid distal portion may vary widely, typically being in the range from 5 mm to 35 mm, more usually from 10 mm to 25 mm, and preferably between 6 mm and 8 mm. In contrast, conventional catheters typically have rigid lengths of approximately 16 mm.

[0081] The side opening windows of the present invention will typically have a length of approximately 2 mm. In other embodiments, however, the side opening cutting window can be larger or smaller, but should be large enough to allow the cutter to protrude a predetermined distance that is sufficient to debulk material from the body lumen.

[0082] The catheters of the present invention can include a flexible atraumatic distal tip coupled to the rigid distal portion of the catheter. For example, an integrated distal tip can increase the safety of the catheter by eliminating the joint between the distal tip and the catheter body. The integral tip can provide a smoother inner diameter for ease of tissue movement into a collection chamber in the tip. During manufacturing, the transition from the housing to the flexible distal tip can be finished with a polymer laminate over the material housing. No weld, crimp, or screw joint is usually required.

[0083] The atraumatic distal tip permits advancing the catheter distally through the blood vessel or other body lumen while reducing any damage caused to the body lumen by the catheter. Typically, the distal tip will have a guidewire channel to permit the catheter to be guided to the target lesion over a guidewire. In some exemplary configurations, the atraumatic distal tip comprises a coil. In some configurations the distal tip has a rounded, blunt distal end. The catheter body can be tubular and have a forward-facing circular aperture which communicates with the atraumatic tip. A collection chamber can be housed within the distal tip to store material removed from the body lumen. The combination of the rigid distal end and the flexible distal tip is approximately 30 mm.

[0084] A rotatable cutter or other tissue debulking assembly may be disposed in the distal portion of the catheter to sever material which is adjacent to or received within the cutting window. In an exemplary embodiment, the cutter is movably disposed in the distal portion of the catheter body and movable across a side opening window. A straight or serrated cutting blade or other element can be formed integrally along a distal or proximal edge of the cutting window to assist in severing material from the body lumen. In one particular embodiment, the cutter has a diameter of approximately 1.14 mm. It should be appreciated however, that the diameter of the cutter will depend primarily on the diameter of the distal portion of the catheter body.

[0085] In exemplary embodiments, activation of an input device can deflect a distal portion of the catheter relative to the proximal portion of the catheter. Angular deflection of the distal portion may serve one or more purposes in various embodiments. Generally, for example, deflection of the distal portion increases the effective "diameter" of the catheter and causes the debulking assembly to be urged against material in a lumen, such as atherosclerotic plaque. In other embodiments, deflection of the distal portion may act to expose a debulking assembly through a window for contacting material in a lumen. In some embodiments, for example, activation of the input device moves the debulking assembly over a ramp or cam so that a portion of the rigid distal portion and flexible tip are caused to drop out of the path of the debulking assembly so as to expose the debulking assembly through the window. In some embodiments, deflection may both urge a portion of the catheter into material in a lumen and expose a tissue debulking assembly.

[0086] It should be understood movement of a tissue debulking assembly may cause deflection of a portion of the catheter or that deflection of the catheter may cause movement or exposure of a tissue debulking assembly, in various embodiments. In other embodiments, deflection of a portion of the catheter and movement of the tissue debulking assembly may be causally unconnected events. Any suitable combination of deflecting, exposing of a debulking assembly and the like is contemplated. In carrying out deflection, exposure and/or the like, a single input device may be used,

so that a user may, for example, deflect a portion of a catheter and expose a tissue debulking assembly using a single input device operable by one hand. In other embodiments, rotation of a tissue debulking assembly may also be activated by the same, single input device. In other embodiments, multiple input devices may be used.

[0087] Some embodiments further help to urge the debulking assembly into contact with target tissue by including a proximal portion of the catheter body having a rigid, shaped or deformable portion. For example, some embodiments include a proximal portion with a bend that urges the debulking assembly toward a side of the lumen to be debulked. In other embodiments, one side of the proximal portion is less rigid than the other side. Thus, when tension is placed on the catheter in a proximal direction (as when pulling the debulking assembly proximally for use), one side of the proximal portion collapses more than the other, causing the catheter body to bend and the debulking assembly to move toward a side of the lumen to be debulked.

[0088] In exemplary embodiments, the debulking assembly comprises a rotatable cutter that is movable outside the window. By moving the cutter outside of the cutting window beyond an outer diameter of the distal portion of the catheter, the cutter is able to contact and sever material that does not invaginate into the cutting window. In a specific configuration, the rotating cutter can be moved over the cam within the rigid, or distal, portion of the catheter body so that the cutting edge is moved out of the window. Moving the rotating cutter outside of the cutting window and advancing the entire catheter body distally, a large amount of occlusive material can be removed. Consequently, the amount of material that can be removed is not limited by the size of the cutting window.

[0089] As will be described in detail below, in some situations it is preferable to provide a serrated cutting edge, while in other situations it may be preferable to provide a smooth cutting edge. Optionally, the cutting edge of either or both the blades may be hardened, e.g., by application of a coating. A preferred coating material is a chromium based material, available from ME-92, Inc., which may be applied according to manufacturer's instructions. In some embodiments, the cutter includes a tungsten carbide cutting edge. Other rotatable and axially movable cutting blades are described in U.S. Pat. Nos. 5,674,232; 5,242,460; 5,312,425; 5,431,673; and 4,771,774, the full disclosures of which are incorporated herein by reference. In some embodiments, a rotatable cutter includes a beveled edge for removal of material from a body lumen while preventing injury to the lumen. In still other embodiments, a tissue debulking assembly may include alternative or additional features for debulking a lumen. For example, the debulking assembly may include, but is not limited to, a radio frequency device, an abrasion device, a laser cutter and/or the like.

[0090] The catheters of the present invention may include a monorail delivery system to assist in positioning the cutter at the target site. For example, the tip of the catheter can include lumen(s) that are sized to receive a conventional guidewire (typically 0.014" diameter) or any other suitable guidewire (e.g., having diameters between 0.018" and 0.032") and the flexible proximal portion of the catheter body can include a short lumen (e.g., about 12 centimeters in length). Such a configuration moves the guidewire out of the rigid portion so as to not interfere with the debulking assembly.

[0091] In other embodiments, however, the guidewire lumen may be disposed within or outside the flexible proximal portion of the catheter body and run a longer or shorter length, and in fact may run the entire length of the flexible portion of the catheter body. The guidewire can be disposed within lumen on the flexible portion of the catheter body and exit the lumen at a point proximal to the rigid portion of the catheter. The guidewire can then enter a proximal opening in the tip lumen and exit a distal opening in the tip lumen. In some embodiments, the catheter has a distal guidewire lumen on its flexible distal tip and a proximal guidewire lumen on its flexible body. For example, in some embodiments the distal lumen may have a length of between about 2.0 cm and about 3.0 cm and the proximal lumen may have a length of between about 10 cm and about 14 cm. In yet further embodiments, a distal tip guidewire lumen may be configured to telescope within a proximal guidewire lumen, or vice versa. A telescoping guidewire lumen may enhance performance of the catheter by preventing a guidewire from being exposed within a body lumen.

[0092] The present invention may optionally employ any of a wide variety of conventional radiopaque markers, imaging devices, and/or transducers. In exemplary embodiments, the catheters of the present invention can include a radiopaque distal portion and/or radiopaque markers disposed on a distal portion of the catheter body, such as proximal and distal of the cutting window, on the cam or ramp, so as to allow the user to track the position of the cutter, or the like. The catheters of the present invention will also be particularly useful with ultrasonic transducers, such as an IVUS, of a type which may be deployed linearly within the catheter body or circumferentially on the debulking assembly. Linear deployment will allow viewing along a discrete length of the catheter axis, preferably adjacent to the cutting point, usually over a length in the range from 1 mm to 30 mm, preferably 2 mm to 10 mm. Circumferentially deployed phased arrays may subtend a viewing arc in the range from 5° to 360°, usually from 180° to 360°. For imaging transducers located on cutting blades within a housing or second cutting element, the field of imaging will generally be limited by the dimensions of the aperture. In some cases, however, it might be possible to fabricate all or a portion of the cutter blade/housing out of an ultrasonically translucent material. A more complete description of suitable imaging catheters are described more fully in U.S. patent application Ser. No. 09/378,224, filed Aug. 19, 1999, and entitled "Atherectomy Catheter with Aligned Imager," now U.S. Pat. No. 6,299,622 B1, the complete disclosure of which is incorporated herein by reference. In addition to ultrasonic array transducers, the imaging devices of the present invention may comprise optical coherence tomography devices, such as described in U.S. Pat. No. 5,491,524, the full disclosure of which is incorporated herein by reference, as well as Huang et al. (1991) Science 254:1178-1181; Brezinski et al. (1997) Heart 77:397-403; and Brezinski et al (1996) Circulation 93:1206-1213. In some instances, the present invention may also provide optical imaging using optical wave guides and the like.

[0093] Referring now to **FIG. 1A**, a catheter **20** constructed in accordance with principles of the present inven-

tion comprises a catheter body **22** having a proximal portion **24** and a distal portion **26**. Proximal portion **24** can be coupled to distal portion **26** with a connection assembly **27** to allow pivoting or deflection of distal portion **26** relative to proximal portion **24**. A proximal end of the catheter body **22** can have a handle **40** for manipulation by a user, a luer for connection to an aspiration or fluid delivery channel, or the like.

[**0094**] A debulking assembly, such as a cutter **28**, abrasive member, or the like, is disposed within a lumen **30** of the catheter body **22**. The cutter **28** is typically rotatable within the distal portion **26** about an axis that is parallel to the longitudinal axis of the distal portion **26** of catheter **20** and axially movable along the longitudinal axis. The cutter **28** can access target tissue through a side opening window **32** which is typically large enough to allow the cutter **28** to protrude through and move out of the window **32** a predetermined distance. The cutter is coupled to a cutter driver **34** through a coiled drive shaft **36**. Actuation of a movable actuator or other input device **38** can activate the drive shaft **36** and cutter, move cutter **28** longitudinally over a cam so as to deflect the distal portion and move the cutter **28** out of cutting window **32**. Camming of the cutter **28** can cause the distal portion **26** to pivot or deflect relative to the proximal portion **24** so as to deflect and urge the cutter into the tissue in the body lumen.

[**0095**] In some embodiments, the distal portion **26** of the catheter may be moved to an angled or offset configuration from the longitudinal axis of the proximal portion **24** of the catheter and the cutter **28**. In some embodiments, the cutter **28** can also be deflected off of the axis of the proximal and/or distal portion of the catheter. Moving the distal portion **26** to an angled/offset position may cause a portion of the catheter to urge against a target tissue, may expose the cutter **28** through the window **32** or both, in various embodiments.

[**0096**] In catheters **20** of the present invention, proximal portion **24** is typically relatively flexible and distal portion **26** is typically relatively rigid. Additionally, many embodiments include a flexible distal tip **42**. The flexible proximal portion **24** of the catheter is typically a torque shaft and the distal portion **26** is typically a rigid tubing. The torque shaft **24** facilitates transportation of the catheter body **22** and cutter **28** to the diseased site. The proximal end of the torque shaft **24** is coupled to a proximal handle **40** and the distal end of the torque shaft is attached to the distal, rigid portion **26** of the catheter through the connection assembly **27**. The drive shaft **36** is movably positioned within the torque shaft **24** so as to rotate and axially move within the torque shaft **24**. The drive shaft **36** and torque shaft **24** are sized to allow relative movement of each shaft without interfering with the movement of the other shaft. The catheter body will have the pushability and torqueability such that torquing and pushing of the proximal end will translate motion to the distal portion **26** of the catheter body **22**.

[**0097**] Referring now to **FIG. 1A**, a catheter **20** as in **FIG. 1A** may have a flexible proximal portion **24** which additionally includes urging means **25**. As shown in **FIG. 1B**, urging means **25** may comprise a rigid bent or curved shape towards the distal end of proximal portion **24**, which may help urge the cutter **28** or other debulking apparatus toward a wall of a body lumen to enhance treatment. Such a rigid bend increases the working range of the catheter by allowing the cutter to be urged into a lumen wall across a wider diameter lumen.

[**0098**] In other embodiments, urging means **25** may take many other suitable forms. For example, a similar result to the rigid bend may be achieved by including a rigid distal portion that is not permanently bent but that is more rigid on one side than on the opposite side of catheter body **22**. Thus, when proximal tension is applied to the proximal portion **24**, as when proximal force is applied to the debulking apparatus to expose the cutter **28** through the window **32**, the urging means **25** (i.e., the rigid distal portion of proximal portion **24**) will cause the catheter body **22** to bend toward the less rigid side. The less rigid side will typically be the same side as the window **32**, so that the window **32** and/or the cutter **28** will be urged against a wall of a body lumen by the bend. In still other embodiments, a shaped element may be introduced into catheter body to act as urging means **25**. Any suitable urging means is contemplated.

[**0099**] **FIG. 2** illustrates an exploded view of a distal end of the catheter. In such embodiments, the catheter **10** includes a connection assembly **27**, a rigid housing **26**, a distal tip **42** that at least partially defines a collection chamber **53** for storing the severed atheromatous material, and a lumen that can receive the guidewire. The distal tip **42** can have a distal opening **43** that is sized to allow an imaging guidewire or conventional guidewire (not shown) to be advanced distally through the tip. In some embodiments, the distal tip **42** may also include a distal guidewire lumen (not shown) for allowing passage of a guidewire. For example, some embodiments may include a distal guidewire lumen having a length of between about 1.0 cm and about 5.0 cm, and preferably between about 2.0 cm and about 3.0 cm. Such a distal guidewire lumen may be used alone or in conjunction with a proximal guidewire lumen located on another, more proximal, portion of the catheter **20**.

[**0100**] In embodiments including a distal guidewire lumen and a proximal guidewire lumen, the distal lumen may be configured to partially telescope within a portion of the proximal guidewire lumen, or vice versa. Such telescoping lumens may be used in embodiments where the distal portion **26** of catheter body **22** is movable relative to the proximal portion **24**. A telescoping lumen may enhance performance of the catheter **20** by allowing a guidewire to be maintained largely within a lumen and to not be exposed within the body lumen being treated. Telescoping lumens may have any suitable diameters and configurations to allow for sliding or otherwise fitting of one lumen within another.

[**0101**] As mentioned above, various embodiments of the invention may allow for deflection of a portion of a catheter, exposure of a tissue debulking assembly through a window, or both. In some embodiments, movement of a tissue debulking assembly causes deflection of a portion of the catheter. In other embodiments, deflection of the catheter may cause a tissue debulking assembly to be exposed through a window on the catheter. In still other embodiments, there may be no causal relationship between deflection of the catheter and exposure of the debulking assembly—i.e., they may be separately caused.

[**0102**] As an example, a ramp or cam **44** may at least partially fit within the distal portion **26**. As will be described in detail below, in some embodiments proximal movement

of the cutter **28** over the ramp **44**, causes the deflection of the distal housing **26** and guides cutter **28** out of cutting window **32**. (In other embodiments, a ramp may be used to deflect the distal portion without extending the cutter out of the window.) Attached to the ramp **44** is a housing adaptor **46** that can connect one or more articulation member **48** to the distal tip to create an axis of rotation of the distal portion **26**. The housing adaptor **46** and articulation member **48** allow the distal end of the catheter to pivot and bias against the body lumen. In the illustrated embodiment there are only one housing adaptor **46** and one articulation member **48**, but it should be appreciated that the catheters of the present invention can include, two, three, or more joints (e.g., axis of rotation), if desired. Moreover, the axes of rotation can be parallel or non-parallel with each other.

[**0103**] The catheter can also include a shaft adaptor **50** and collar **52** to couple articulation member **48** to the torque shaft **22**. Shaft adaptor **50** can connect the housing to the torque shaft and collar **52** can be placed over a proximal end of the shaft adaptor and crimped for a secure attachment. It should be appreciated by one of ordinary skill in the art that that while one exemplary catheter of the present invention has the above components that other catheters of the present invention may not include more or fewer of the components described above. For example, some components can be made integral with other components and some components may be left out entirely. Thus, instead of having a separate ramp **44**, the ramp may be integrated with the distal tip to direct the cutter out of the cutting window.

[**0104**] As shown in **FIGS. 3-5**, the cutters **28** of the present invention will generally be movable between two or more positions. During advancement through the body lumen, the cutter will generally be in a neutral position (**FIGS. 3A and 3B**) in which the cutter **28** is distal of cutting window **32**. In some embodiments, an imaging device (not shown) can be coupled to cutter **28** so as to image the body lumen through cutting window **32** when cutter **28** is in the neutral position. Once the catheter **20** has reached the target site, the cutter **28** can be moved to an open position (**FIGS. 4A and 4B**) in which the cutter **28** is moved to a proximal end of the cutting window **32** and will extend out of the cutting window **32** a distance L**1** beyond an outer diameter D of the rigid portion **26**. In most embodiments, in the open position, the cutter will have deflected the distal portion and the cutter's axis of rotation will generally be in line with connection assembly **27** but angled or offset from longitudinal axis of the distal portion of the catheter body.

[**0105**] Optionally, in some embodiments, cutter **28** can be moved to a packing position, in which the cutter is moved distally, past the neutral position, so as to pack the severed tissue into a distal collection chamber **53** (**FIGS. 5A and 5B**). It should be appreciated however, that while the exemplary embodiment moves the cutter to the above described positions, in other embodiments of the present invention the cutter can be positioned in other relative positions. For example, instead of having the neutral position distal of the cutting window, the neutral position may be proximal of the window, and the open position may be along the distal end of the cutting window, or the like.

[**0106**] Referring again to **FIGS. 4A and 4B**, the interaction of the components of the rigid distal portions **26** in one exemplary embodiment of the present invention will be further described. As shown in **FIG. 4B**, the cutting window **32** is typically a cutout opening in the distal portion **26**. While the size of the cutting window **32** can vary, the cutting window should be long enough to collect tissue and circumferentially wide enough to allow the cutter to move out of the cutting window during cutting, but sized and shaped to not expel emboli into the vasculature. Cams or ramp **44** (shown most clearly in **FIG. 4B**) can be disposed in the distal portion of the catheter body to guide or otherwise pivot the cutter **28** out of the cutting window **32** as the cutter **28** is pulled proximally through tensioning of drive shaft **36**.

[**0107**] A joint is located proximal to the cutting window **32** to provide a pivot point for camming of the distal portion **26** relative to the proximal portion **24**. The bending at a flexible joint **49** is caused by the interaction of cams or ramps **44** with cutter **28** and the tensile force provided through drive shaft **36**. In the exemplary configuration, the joint includes a housing adaptor **46** that is pivotally coupled to the distal rigid portion **26**. As shown in **FIGS. 4A and 4B**, the resulting pivoting of the rigid distal portion **26** relative to the proximal portion causes a camming effect which urges the distal housing against the body lumen wall without the use of urging means (e.g., a balloon) that is positioned opposite of the cutting window. Thus, the overall cross sectional size of the catheter bodies can be reduced to allow the catheter to access lesions in smaller body lumens. In exemplary embodiments, the distal housing can deflect off of the axis of the proximal portion of the catheter typically between 0° degrees and 300 degrees, usually between 5° degrees and 20° degrees, and most preferably between 5° degrees and 10° degrees. The angle of deflection relates directly to the urge. Urge, however, does not necessarily relate to force but more to the overall profile of the catheter. For example, the greater the angle of deflection, the larger the profile and the bigger the lumen that can be treated. The ranges were chosen to allow treatment of vessels ranging from less than 2 mm to greater than 3 mm within the limits of mechanical design of the components. It should be appreciated however, that the angles of deflection will vary depending on the size of the body lumen being treated, the size of the catheter, and the like.

[**0108**] In some embodiments, the deflection of the distal portion **26** of the catheter urges the cutter into position such that distal advancement of the entire catheter body can move the rotating cutter through the occlusive material. Because the cutter is moved a distance L**1** beyond the outer diameter of the distal portion of the catheter and outside of the cutting window, the user does not have to invaginate the tissue into the cutting window. In some embodiments, for example, the cutter can be moved between about 0.025 mm and about 1.016 mm, and preferably between about 0.025 mm and about 0.64 mm, beyond the outer dimension of the distal housing. It should be appreciated that the cutter excursion directly relates to the depth of cut. The higher the cutter moves out of the cutting window the deeper the cut. The ranges are chosen around efficacy without risk of perforation of the body lumen.

[**0109**] Some embodiments of the catheter include a shuttle mechanism or other similar mechanism for temporarily locking the catheter in a cutting position. **FIGS. 3C and 3D** illustrate such an embodiment in the neutral, non-cutting position. Such embodiments generally include a shuttle member **45** and a shuttle stop member **42**. The shuttle stop

member **42** is typically disposed at an angle, relative to a longitudinal axis through the catheter. **FIGS. 4C and 4D** show the same embodiment in the cutting position. When the cutter **28** is moved into the cutting position in such embodiments, the shuttle member **45** falls into the shuttle stop member **42** and thus locks the debulking apparatus in a cutting position. To unlock the debulking apparatus, the cutter **28** may be advanced forward, distally, to release the shuttle member **45** from the shuttle stop member **42**.

[**0110**] Some embodiments including a shuttle mechanism will also include two joints in catheter body **22**. Thus, catheter body **22** will include a proximal portion **26**, a distal portion **24** and a middle portion. When shuttle mechanism is activated to expose cutter **28** through window **32**, the middle portion may orient itself at an angle, relative to the proximal and distal portions, thus allowing cutter to be urged towards a side of a lumen. Such a two jointed configuration may provide enhanced performance of the catheter **20** by providing enhanced contact of the cutter **28** with material to be debulked from a body lumen.

[**0111**] Pushing the entire catheter across a lesion removes all or a portion of the lesion from the body lumen. Severed tissue from the lesion is collected by directing it into a collection chamber **53** in the tip via the cutter **28**. Once the catheter and cutter **28** have moved through the lesion, the cutter **28** can be advanced distally to a "part off position" in which the cutter is moved back into the cutting window **32** (**FIG. 3B**). The tissue is collected as the severed pieces of tissue are directed into a collection chamber **53** via the distal movement of cutter **28** and catheter. The collection chamber **53** of the tip and distal portion **26** acts as a receptacle for the severed material, to prevent the severed occlusive material from entering the body lumen and possibly causing downstream occlusions. The cutter **28** can interact with the distal edge of the cutting window to part off the tissue and thereafter pack the severed tissue into collection chamber **53** (**FIG. 3B**). In exemplary embodiments, the driver motor can be programmed to stop the rotation of the cutter at the part off position so that the cutter **28** can move to a third position (**FIG. 5B**) and pack the material in the collection chamber in the tip without rotation. Typically, the collection chamber **53** will be large enough to allow multiple cuts to be collected before the device has to be removed from the body lumen. When the collection chamber is full, or at the user's discretion, the device can be removed, emptied and reinserted over the guidewire via a monorail system, as will be described below.

[**0112**] In various embodiments, enhancements to the collection chamber **53** may be included. For example, in some embodiments the collection chamber **53** may be configured to be partially or completely translucent or radiolucent and a portion of the catheter surrounding or adjacent to the window **32** will be radiopaque. This combination of radiolucent collection chamber **53** and radiopaque material adjacent window **32** will enhance the ability of a user to determine how full the collection chamber **53** is, because the fullness of the collection chamber will be directly related to the distance the cutter **28** can advance forward into the collection chamber **53**. By facilitating the assessment of collection chamber filling, these embodiments will reduce the need for manually withdrawing the catheter to examine the collection chamber **53**.

[**0113**] In some embodiments, the collection chamber **53** may connect to the rigid housing by means of interlocking components, which interlock with complementary components on the rigid housing. Such components may resemble a screw-in configuration, for example. Interlocking components will provide a stable connection between the collection chamber **53** and the rigid housing while not increasing the outer diameter of either the chamber **53** or the housing. Generally, collection chamber **53** may be given any suitable configuration, shape or size. For example, collection chamber **53** in **FIGS. 6-8** has a helical configuration. Alternatively, collection chamber **53** may include a series of circular members, straight linear members, one solid cylindrical or cone-shaped member or the like.

[**0114**] **FIGS. 6 through 8** illustrate one exemplary monorail delivery system to assist in positioning the cutter **28** at the target site. For example, tip **42** of the catheter can include a lumen **54** having a distal opening **43** and a proximal opening **55** that is sized to receive a guidewire, having a diameter of about 0.014 in., about 0.018 in., about 0.032 in. or any other suitable diameter.

[**0115**] As shown in **FIG. 8**, the flexible proximal portion of the catheter body may also include a short lumen **56** (e.g., about 12 centimeters in length). In some embodiments, however, the guidewire lumen **56** may be disposed within or outside the flexible proximal portion of the catheter body and run a longer or shorter length, and in fact may run the entire length of the flexible portion **24** of the catheter body. In use, the guidewire can be disposed within lumen **56** on the flexible portion of the catheter body and exit the lumen at a point proximal to the rigid portion **26** of the catheter. The guidewire can then re-enter a proximal opening **55** in the tip lumen **54** and exit through distal opening **43** in the tip lumen. By moving the guidewire outside of the rigid portion **26** of the catheter body, the guidewire will be prevented from tangling with the cutter **28**. Typically, tip lumen **54** will be disposed along a bottom surface of the tip and the lumen **56** will be disposed along a side of the proximal portion **22** of the catheter body so that the guidewire will be in a helical configuration. In various embodiments, the tip lumen **54** and the proximal lumen **56** can have any suitable combination of lengths. For example, in one embodiment the tip lumen **54** may have a length between about 1 cm and about 5 cm, more preferably between about 2 cm and about 3 cm, and the proximal lumen may have a length of between about 8 cm and about 20 cm, more preferably between about 10 cm and about 14 cm.

[**0116**] Referring now to **FIGS. 22A and 22B**, some catheters **120** of the present invention include a proximal guidewire lumen **126** coupled with the proximal portion of the catheter body **123**, and a telescoping distal guidewire lumen **124** coupled with either the distal tip **122**, part of the distal portion of the catheter body, or both. The telescoping lumen **124** will typically be attached to the tip **122** or a distal portion, but will also include an unattached portion **121**, which will not be directly attached to any part of the catheter body. This unattached portion **121** (or "free floating lumen") protects a guidewire from contacting a body lumen in which the device is used and also allows the device to be moved more freely, without bending or kinking the guidewire. The telescoping guidewire **124** extends within the proximal lumen **126** at the distal opening **127** of proximal lumen **126**. Again, the telescoping feature allows for movement of the

catheter body while preventing or reducing bending of the guidewire. For example, in some embodiments catheter **120** allows for deflection of distal tip **122** and the distal portion of the catheter **120** relative to the proximal portion **123**, for example by movement about a pivot point **129**. Telescoping distal lumen **124** and proximal lumen **126** allow for this movement by allowing distal lumen **124** to telescope within proximal lumen **126**. At the same time, distal lumen **124** protects a guide wire from exposure to a body lumen and/or bodily fluids.

[**0117**] Any suitable configurations and sizes of distal lumen **124** and proximal lumen **126** are contemplated. For example, in one embodiment distal lumen **124** may telescope within proximal lumen **126** by a distance of approximately I cm. Furthermore, a telescoping lumen **124** may be longer than distal lumens in other embodiments. For example, telescoping lumen **124** may have a length of between about 2 cm and about 10 cm, and preferably between about 5 cm and about 8 cm. As is apparent from the drawing figures, the outer diameter of telescoping distal lumen **124** is configured to fit within the inner diameter of proximal lumen **126**. Generally, any combination of sizes, lengths, diameters and shapes of distal lumen **124** and proximal lumen **126** may be used, to allow telescoping of one into another.

[**0118**] The catheters of the present invention can include radiopaque markers so as to allow the user to track the position of the catheter under fluoroscopy. For example, as already described, a point or area around or adjacent to the window may be made radiopaque. In other embodiments, the rigid distal portion **26** can be radiopaque and radiopaque markers can be disposed on the flexible shaft. Typically, the markers **59** will be disposed along the top, proximal to the cutting window, and on the bottom of the catheter to let the user know the position of the cutter and cutting window relative to the target site. If desired, the top and bottom markers can be different shaped so as to inform the user of the relative orientation of the catheter in the body lumen. Because the guidewire will form a helix in its transition from lumen **56** to tip lumen **54**, the user will be able to view the top and bottom radiopaque markers **59** without interference from the guidewire. Some embodiments of the catheter can also include a radiopaque cutter stop **61** (**FIG. 3B**) that is crimped to driveshaft **36** proximal of the cutter that moves with the cutter so as to let the user know when the cutter is in the open position.

[**0119**] **FIGS. 9A through 11D** show some exemplary embodiments of the cutter **28** of the present invention. The distal portion **60** of the rotatable cutter **28** can include a serrated knife edge **62** or a smooth knife edge **64** and a curved or scooped distal surface **66**. The distal portion **60** may have any suitable diameter or height. In some embodiments, for example, the diameter across the distal portion **60** may be between about 0.1 cm and about 0.2 cm. A proximal portion **68** of the cutter **28** can include a channel **70** that can be coupled to the drive shaft **36** that rotates the cutter. As shown in **FIGS. 10A-10C**, some embodiments of the cutters can include a bulge or bump **69** that is provided to interact with a stent so as to reduce the interaction of the cutting edge with the stent. In any of the foregoing embodiments, it may be advantageous to construct a serrated knife edge **62**, a smooth knife edge **64**, or a scooped distal surface **66** out of tungsten carbide.

[**0120**] Another embodiment of a cutter **28** suitable for use in the present invention is shown in side view within a catheter body distal portion **26** in **FIG. 11D**. In this embodiment, the cutter **28** has a beveled edge **64**, made of tungsten carbide, stainless steel, titanium or any other suitable material. The beveled edge **64** is angled inward, toward the axis of rotation (or center) of the cutter **28**, creating a "negative angle of attack"**65** for the cutter **28**. Such a negative angle of attack may be advantageous in many settings, when one or more layers of material are desired to be debulked from a body lumen without damaging underlying layers of tissue. Occlusive material to be removed from a vessel typically has low compliance and the media of the vessel (ideally to be preserved) has higher compliance. A cutter **28** having a negative angle of attack may be employed to efficiently cut through material of low compliance, while not cutting through media of high compliance, by allowing the high-compliance to stretch over the beveled surface of cutter **28**.

[**0121**] **FIGS. 12 through 16** illustrate an exemplary cutter driver **34** of the present invention. As shown in **FIG. 12** and **13**, cutter driver **34** can act as the handle for the user to manipulate the catheters **20** of the present invention as well as a power source. Typically, the cutter drivers **34** of the present invention include a single input device, such as a lever **38** that controls the major operations of the catheter (e.g., axial movement to cause urging, rotation to cause cutting, and axial movement for packing). As shown in **FIGS. 13 and 14**, cutter driver **34** includes a power source **72** (e.g., batteries), a motor **74**, a microswitch **76** for activating motor **74**, and a connection assembly (not shown) for connecting the drive shaft **36** to the driver motor **74**. In some embodiments, the drive motor can rotate drive shaft **36** between 1,000 rpm and 10,000 rpm or more, if desired.

[**0122**] **FIGS. 14 through 16** illustrate one exemplary method of operating cutter driver **34**. In use, the catheter will be delivered to the target site with cutter driver unattached and the cutter in the neutral position (**FIG. 3B**). The cutter driver can be attached with the urge lever **38** in a neutral position (**FIG. 14**), which indicates that the cutter is closed, but not in a packing position. The user can then move the catheter (and cutter driver unit, if desired) to position the distal portion **26** of the catheter adjacent the target tissue. As shown in **FIG. 15**, to activate the rotation of the cutter, the urge lever **38** can be moved proximally from the neutral position to move the cutter proximally and out of cutting window **32** (**FIG. 4B**) and simultaneously depressing microswitch **76** to activate motor **74**. At the end of the cutting procedure, as shown in **FIG. 16**, the user can push urge lever **38** completely forward to a distal position to push the cutter into a packing position (**FIG. 5B**). After the urge lever passes the middle of the travel, the microswitch **76** can be released so as to deactivate the cutter before reaching the packing position such that packing can occur without the cutter rotating. It should be appreciated, while the figures illustrate the use of an urge lever or thumb switch as an input device, the present invention can use other type of input devices, such as labeled buttons (e.g., close window, debulk tissue, and pack), or the like.

[**0123**] Advantageously, cutter driver **34** provides an automatic on/off control of the cutter **28** that is keyed to the position of the cutter. Such a configuration frees the user

from the complicated task of remembering the sequence of operations to activate and deactivate the rotation and axial movement of the cutter.

[0124] While the cutter driver **34** is illustrated as a disposable battery powered unit, it should be appreciated that in other embodiments, the cutter driver can use other power sources to control the cutter driver. It should further be appreciated that other cutter drivers can be used with the present invention. While not preferred, it is possible to have separate controls to control the axial movement of the cutter and the rotation of the cutter.

[0125] Some exemplary methods of the present invention will now be described. One method of the present invention comprises delivering a catheter to a target site in the body lumen. A distal portion of the catheter can be deflected relative to a proximal portion of the catheter to expose a tissue debulking device in the catheter. The body lumen can be debulked with the exposed debulking device. Specifically, as shown schematically in **FIG. 17**, one specific method comprises advancing a catheter to a target site (Step **100**). A cutter can be rotated and moved out of the cutting window (Steps **102**, **104**). Preferably, a distal portion of the catheter can be pivoted or deflected so as to position the cutter adjacent the target material. Thereafter, the catheter and the rotating cutter can be moved through the body lumen to remove the target material from the body lumen (Step **106**).

[0126] As shown in **FIGS. 18 and 19**, the catheter can be percutaneously advanced through a guide catheter or sheath and over a conventional or imaging guidewire using conventional interventional techniques. The debulking catheter **20** can be advanced over the guidewire and out of the guide catheter to the diseased area. As shown in **FIG. 18**, the window **32** will typically be closed (with the cutter or other debulking device **28** in a first, distal position). As shown in **FIG. 19**, catheter **20** will typically have at least one hinge or pivot connection to allow pivoting about one or more axes of rotation to enhance the delivery of the catheter into the tortuous anatomy without dislodging the guide catheter or other sheath. The cutter can be positioned proximal of the lesion. Optionally, a transducer, IVUS, or other imaging assembly can be used to verify the position of the debulking catheter.

[0127] Once the position of the catheter is confirmed, the cutter **28** will be retracted proximally and moved out of cutting window **32** to its second, exposed position. In some embodiments, movement of the cutter can deflect the distal portion of the catheter to increase the profile of the catheter at the target site. Movement of the cutter is typically caused by proximal movement of lever **38** and tensioning of drive shaft **36**. Movement of the lever can be scaled to any desired ratio or a direct 1:1 ratio of movement between the handle and cutter. When the cutter is moved proximally it contacts ramp or cam surfaces so as to guide the cutter up and at least partially out of the cutting window **32**. Additionally, as shown by arrow **80**, the distal portion of catheter body **26** rotates about the joint **49** to provide an urging force for the cutter (and catheter body) to move toward the diseased area.

[0128] Thereafter, as shown by arrow **82** the operator can move the entire catheter body **22** through the lesion to dissect the tissue. As the cutter **28** and catheter body **22** are advanced distally through the lesion, tissue that is trapped between the cutting edge **52** and the cutting window **32** is severed from the body lumen. To part off the tissue, the operator can stop pushing the device distally and the cutter can be advanced distally inside the cutting window by advancing the handle **38**. During the distal movement of the cutter, the cutter **28** rides back over the ramps **44** and directs the cutter back inside of the cutting window **32**. Such movement causes the distal portion **26** of the catheter to move in line with the cutter and proximal portion **24** (**FIG. 5B**). When the cutter has moved to its distal position, the cutter parts off the severed tissue and urges the severed tissue inside of a collection chamber **53** in the distal tip **42**. Optionally, after the cutter **28** has parted off the tissue, the lever **38** and thus the non-rotating cutter **38** can be advanced distally to pack the tissue into the collection chamber **53** (**FIG. 5B**). Use of the cutter to pack the severed tissue will allow the operator multiple specimens to be collected prior to removing the catheter **20** from the body lumen. When it is determined that the collection chamber is full, the catheter can be removed from the body lumen and the collection chamber can be emptied, and the excised tissue may be stored or tested as described above.

[0129] In another method of the present invention, as shown in **FIG. 20**, an input device is disposed in a first position to position a tissue removal element in a neutral position (Step **120**). The input device is activated to rotate the tissue removal element and to axially move the tissue removal device to an active position (Step **122**). The input device can then be activated again to move the tissue removal element to a packing position (Step **124**). In an exemplary embodiment, the input device is a lever or thumb switch that can be moved to correspond to the movement of a cutting element on the catheter. Thus, as the lever is moved proximally, the cutter is rotated and moved proximally to an open position. When the lever is moved to a distal position, the rotation of the cutter can be stopped and the cutter can be moved distally to pack severed tissue into a collection chamber.

[0130] Referring now to **FIG. 21**, the present invention will further comprise kits including catheters **200**, instructions for use **202**, and packages **204**. Catheters **200** will generally be as described above, and the instruction for use (IFU) **202** will set forth any of the methods described above. Package **204** may be any conventional medical device packaging, including pouches, trays, boxes, tubes, or the like. The instructions for use **202** will usually be printed on a separate piece of paper, but may also be printed in whole or in part on a portion of the packaging **204**.

[0131] **FIG. 23** depicts gross samples of plaque tissue removed from the left leg (left side of **FIG. 23**) and the right leg (right side of **FIG. 23**) taken from a plurality of different patients. Five patients in the bilateral study described in Example **1** (described below) yield plaque material from each leg. For each patient, the plaque tissue has similar appearance in both the left leg and right leg. The gross appearance of the material from each leg, in comparison to the other leg indicates no reason the material could not be considered comparable and testable, one in comparison to the other.

[0132] **FIG. 24** illustrates the histological staining of lipid deposit (trichrome), CD 68, CRP, and Lp-PLA2 in a single

patient. The protein content in the sample, while not quantified, indicates the presence of the proteins or lipids in the sample.

[0133] **FIG. 25** presents data from **5** patients indicating by positive staining in the left versus the right leg the presence "+" or absence of "−" Lipid deposit, CD68, CRP, and Lp-PLA2. The majority of left and right legs samples are in agreement in the immunohistochemistry results that indicate the presence or absence of a particular protein or molecule.

[0134] **FIG. 26** presents gene array data from plaque excised from both right and left legs of several patients. The data supports that the plaque from both appendages is comparable one unto the other and therefore potentially useful for testing the efficacy of a drug or biological agent using gene array information to make an evaluation of efficacy.

EXAMPLE 1

Bilateral Appendage Comparison of Protein Content in Resected Arterial Plaque

[0135] For this study five patients with peripheral arteriolosclerosis were selected. Plaque tissue was removed from both legs in all patients. See **FIG. 23** for images of the gross tissue mass removed. Some of the removed tissue was frozen. For analysis some of the frozen tissue was thawed and fixed with **10**% formalin and subjected to routine paraffin processing. Five micron sections were cut, stained with elastic and Trichrome collagen stains and these slides were microscopically evaluated for general histology. **FIG. 24** illustrates the histological results and **FIG. 25** designates for the 5 patients the presence or absence of lipid deposits, and the proteins: CD68, CRP, and Lp-PLA2. Only the last patient (BAKCA) had some discordance between the stained protein content, the rest of the patients had the same lipid and protein levels as measured by immunohistochemistry in both their left and right legs. Gene array information was yielded from testing the material in the right and left legs of the patients (see **FIG. 26**).

EXAMPLE 2

[0136] Tissue extraction and preparation is conducted as described in Example 1. The isolated tissue is analyzed for the following protein markers using standard techniques known in the art: interleukin-18, RANTES, fractalkine, interleukin-1-beta, matrix metalloproteinase-9, tumor necrosis factor-alpha, monocyte inflammatory protein alpha, E-selectin and P-selectin.

[0137] While all the above is a complete description of the preferred embodiments of the inventions, various alternatives, modifications, and equivalents may be used. For example, while preferred cutters are moved proximally to move the cutter out of the cutting window, alternative embodiments may move the cutter distally to move the cutter out of the cutting window. Additionally, while most embodiments employ a cutter that extends out beyond the outer diameter of the cutting window, it may be possible to incorporate a cutter that stays within the diameter catheter body. Additionally, in some embodiments, the debulking assembly may be exposed through the window without causing a deflection of the distal portion of the catheter. Moreover, instead of having a distal tip that is rotatable relative to the proximal portion of the catheter, the catheter can include a shape memory material such that the catheter forms a jog or a pre-bent shape when it reaches its target area. Although the foregoing invention has been described in detail for purposes of clarity of understanding, it will be obvious that certain modifications may be practiced within the scope of the appended claims.

What is claimed is:

1. A method of evaluating a treatment of a patient having vascular disease comprising the steps of:

removing a first sample of tissue from a vascular lumen of the patient;

analyzing at least one property of the tissue;

administering a treatment to the patient;

removing a second sample of tissue from a vascular lumen of the patient,

analyzing the at least one property of the second sample,

comparing properties of the first and second samples to determine an effect of the treatment on the patient.

2. The method of claim I wherein the property is selected from the group consisting of: presence of a marker, level of a marker, modification of a marker, activity of a protein, activity of an RNA, transcription, translation, ligand binding, cellular activity, proliferation, inflammation, and infection.

3. The method of claim 1 wherein the first and the second samples are removed from a first site.

4. The method of claim 1 wherein the first sample is removed from a first site and the second sample is removed from a second site.

5. The method of claim 1 wherein said first and second samples are removed from first and second appendages.

6. The method of claim 5 wherein the first and second appendages are legs.

7. The method of claim 5 wherein the first and second appendages are arms.

8. The method of claim 4 wherein the first and second sites are in peripheral vasculature.

9. The method of claim 4 wherein the first and second sites are in coronary vasculature.

10. The method of claim 4 wherein the first and second sites are in arteries.

11. The method of claim 4 wherein one of the first and second sites is in peripheral vasculature, and the other is in coronary vasculature.

12. The method of claim 1 wherein the samples are removed by percutaneous surgical excision of tissue using an atherectomy catheter.

13. The method of claim 2 wherein said property is the presence of a marker and the marker is selected from the group consisting of a nucleic acid marker and a protein marker.

14. The method of claim 2 wherein the property is the presence of a marker and the marker is selected from the group consisting of: a growth factor, a growth factor receptor, an apoptotic marker, a cell-cycle protein, a transcriptional regulator, a proliferative marker, an adhesion molecule, a cytokine, a chemokine, a chemokine receptor, a coagulation factor, a fibrinolytic marker, an oxidative stress related molecule, and an extracellular matrix marker.

15. The method of claim 1 wherein the treatment is an agent selected from the group consisting of a plaque-reducing agent, an anti-inflammatory agent, an enzyme inhibitor, a protein synthesis inhibitor, an inhibitor of cell proliferation, a transcription factor inhibitor, a lipid transport molecule, a cholesterol-reducing agent, a thrombolytic molecule, a signal inhibitor, an anti-platelet molecule, a kinase inhibitor, and a statin drug.

16. The method of claim 1 wherein more than one treatment is administered to the patient in combination.

17. The method of claim 1 wherein the treatment comprises placing a foreign object in the patient.

18. The method of claim 17 wherein the foreign object comprises a prosthetic device.

19. The method of claim 18 wherein the prosthetic device is a stent.

20. The method of claim 18 wherein the samples are removed by percutaneous surgical excision of the tissue using an atherectomy catheter.

21. A method of evaluating an effect of a treatment on a patient having vascular disease comprising the steps of:

removing tissue from a site in a vascular lumen in a patient;

administering a treatment to the patient;

monitoring the patient for recurrence of the tissue at the site in the vascular lumen,

identifying an effect of the treatment if the tissue does not recur at the site.

22. The method of claim 21 wherein said monitoring comprising imaging.

23. The method of claim 22 wherein said imaging comprises an imaging methodology selected from the group consisting of sonography, radiography, magnetic resonance imaging, angiography, and fluoroscopy.

24. The method of claim 21 wherein the tissue comprises plaque.

25. The method of claim 21 wherein the tissue comprises an atheroma.

26. The method of claim 21 wherein the treatment is selected from the group consisting of: systemic administration of an agent, introduction of a prosthesis into the vascular lumen, administration of externally sourced energy to the subject, and local administration of an agent to the site of tissue removal.

27. The method of claim 21 wherein the treatment is introduction of a prosthesis and the prosthesis is a stent.

28. The method of claim 21 wherein the tissue is removed by percutaneous surgical excision of vascular tissue using an atherectomy catheter.

29. The method of claim 21 wherein the treatment is a test agent selected from the group consisting of a plaque-reducing agent, an anti-inflammatory agent, an enzyme inhibitor, a protein inhibitor, an inhibitor of cell proliferation, a transcription factor inhibitor, a lipid transport molecule, a cholesterol target molecule, a thrombolytic molecule, a signal inhibitor, an anti-platelet molecule, a kinase inhibitor, and a statin.

30. The method of claim 29 wherein more than one test agent is administered in a combination.

31. A method of determining if a test molecule localizes in tissue in a vascular lumen, comprising the steps of:

introducing a test molecule having a detectable tag into vasculature of a patient having vascular disease;

removing a sample of tissue from a vascular lumen of the patient;

determining the presence and/or amount of the test molecule having the detectable tag in the tissue.

32. The method of claim 31 wherein the detectable tag is a moiety selected from the group consisting of a radioactive moiety, a fluorescent moiety, an antibody, a ligand, and an enzyme.

33. A method of evaluating a treatment of a patient having vascular disease, comprising the steps of:

introducing an atherectomy catheter percutaneously in the patient and directing the catheter to a first site in a vascular lumen containing tissue;

removing a first sample of tissue from the vascular lumen of the patient;

analyzing at least one property of the vascular tissue;

administering a treatment to the patient;

reintroducing an atherectomy catheter percutaneously in the patient and directing the catheter to a second site in a vascular lumen containing tissue;

removing a second sample of tissue from vascular lumen of the patient,

analyzing the at least one property of the second sample,

comparing properties of the first and second samples to determine an effect of the treatment on the patient.

34. The method of claim 33 wherein the atherectomy catheter comprises a rotating cutter, a collection chamber, and a cutting window, the rotating cutter being movable between a stored position and an exposed position; said method further comprising:

exposing the cutter by moving the cutter to the exposed position after introducing the atherectomy catheter to the vascular lumen;

advancing the catheter to move the rotating cutter through the vascular tissue in the first site, the rotating cutter remaining in the exposed position so that the cutter and the window maintain their orientation with respect to one another when advancing, wherein the vascular tissue is directed through the cutting window and into the collection chamber as the catheter is advanced, and

removing the vascular tissue from the collection chamber.

35. The method of claim 34, further comprising:

moving the cutter to the stored position prior to removing the vascular tissue from the collection chamber;

repositioning the catheter at a second site in a vascular lumen;

exposing the cutter by moving the cutter to the exposed position;

advancing the catheter to move the rotating cutter through vascular tissue in the second site, the rotating cutter remaining in the exposed position so that the cutter and

the window maintain their orientation with respect to one another when advancing, the vascular tissue cut by the rotating cutter being directed through the cutting window and into the collection chamber as the catheter is advanced.

36. The method of claim 2 wherein the property is the presence of a marker and the marker is selected from the group consisting of: interleukin-18, RANTES, fractalkine, interleukin-1-beta, matrix metalloproteinase-9, tumor necrosis factor-alpha, monocyte inflammatory protein alpha, E-selectin and P-selectin.

37. The method of claim 36 wherein the marker is a peptide, polypeptide, or protein.

38. The method of claim 36 wherein the marker is a nucleic acid.

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